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ALLERGENICITY OF MODIFIED AND PROCESSED FOODSTUFFS

I. The Use of a Dual Ingestion Passive Transfer Test to Determine the Allergenicity of Foodstuffs in Man

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WE DEMONSTRATED in animals, by the use of the anaphylaxis method, that certain heat treated and processed foodstuffs were reduced in anaphylactogenicity.[8,9,10] Randolph[7] agreed with and corroborated our animal experiments that sugar syrup and crystalline sugar derived from the hydrolysis of corn were non-anaphylactogenic for guinea pigs. He did not, however, agree with our deductions regarding their clinical significance in man.

He and others have subsequently reported upon clinical observations in human subjects relative to allergenicity of heated foods, edible oils and refined sugars. The technique employed was to determine by clinical trials whether foodstuffs taken orally would induce allergic reactions.

The first to initiate such an investigation was Rowe,[13] who employed elimination diets. Certain suspected foods are eliminated from the patient's diet until he is symptom-free. After a period of time, one of the suspected foods is returned to the diet, and if an exacerbation of symptoms occurs, the conclusion is that the patient is sensitive to that food. As can readily be seen the method is complex, and it really becomes a herculean task on the part of both patient and physician to track down sensitivities in this fashion. Other criticisms can be leveled at this procedure, but for the purposes of our discussion it is not necessary to go into them. Results have been far from satisfactory. Vaughan[14] used the trial diet to determine the leukopenic index. This method has been of questionable value.

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More recently Rinkel[11] has devised a method, based on the ingestion test, in which there are three stages: 1) a period of two weeks during which the test food is ingested; 2) a succeeding period of four days of abstinence from the test food; 3) the morning following this period of abstinence the test food is ingested on a fasting stomach and the resulting signs and symptoms are observed. This test has been used extensively by Randolph.

Both Rinkel and Randolph[6] include as positive reactions such signs as coughing, headache, nasal symptoms, clearing of the throat, itching of the skin—particularly under the chin or nose—a sensation of pulling or drawing tightness in the back of the neck, chill and goose flesh, abdominal pain, cramps, diarrhea, vomiting, tachycardia, perspiration, stretching and fatigue. This is all covered in their book.[12]

In my estimation such an investigation is subject to criticism on several counts. The authors do not present enough objective proof of the presence of food allergy in their patients. They do not always use skin tests or other accepted criteria. The test technique itself is very rigorous and whether a patient is sensitive or not, it seems to me he may react in one of the many ways described. Many of the symptoms are certainly subjective, and I find it difficult to believe that they can always be accepted as criteria consonant with experimental data.

The masked ingestion test of Loveless[3,4] is more objective. She substitutes other substances bearing some resemblance to the food in question. Furthermore, she includes as reactions only objective findings that are generally regarded as allergic in nature. The blindfold test of Bernton[1,2] in which the patient does not know which oil he is ingesting, may also be classified as objective. Yet, tests of this nature do present difficulties in interpretation.

Since some have objected to the application of our findings in the animal to the human subject, and since we have been critical of the clinical observations reported in the literature, it seemed essential to devise a method that would fulfill criteria for scientific accuracy, and yet could be carried out on the human subject. To pursue investigations on the allergenicity of modified and processed foodstuffs as they affect man, in contrast to foods in native form and that would stand up to scientific standards, we would have to devise a test that neither the patient nor the investigator could influence.

The method which we finally conceived is based on the use of a human subject who is clinically sensitive to the food to be studied, who gives a positive skin reaction to it, and who also possesses specific circulating antibodies to it.

The tests with the food in native and modified forms are not performed on the patient by oral trial, but instead upon non-allergic recipients. No symptomatology that may be subjective in nature is sought for. The

objective finding of a positive urticarial reaction at passively sensitized sites in the recipient is the sole determinant of the reaction. We believe that the method to be described offers an objective approach to the problem in the human subject. It has the added advantage that it offers the opportunity of studying the degree and character of the allergenicity of modified and processed foodstuffs.

This method is an extension of the Prausnitz-Küstner passive transfer test,[5] and the indirect modification of it by Walzer.[15] We think an appropriate name for it is the Dual Ingestion Passive Transfer Test. The experiment has three phases. The first one relates to the donor, the second to the recipients and the final phase is the test itself.

DUAL INGESTION PASSIVE TRANSFER TEST

I. *Donor.*—Allergic subjects with a negative history for virus hepatitis and syphilis are tested with food allergens. Those found skin-sensitive to food proteins, and who are clinically sensitive to them as well, are used as potential donors.

Serum is separated from the blood drawn, and tested for sterility. It is then promptly frozen and/or lyophilized. When reconstituted it is ready for use.

II. *Recipients.*—Preferably non-allergic subjects are selected as recipients. They are skin-tested to rule out hypersensitivity to the substances under investigation.

Throughout the test period all of the foods to which the donor reacts must be completely eliminated from the recipient's diet.

III. *Test.*—The donor serum is injected into several skin sites of the recipient to produce passive sensitization.

To determine whether the donor serum contains specific circulating allergic antibodies to the foodstuffs under investigation, one of the passively sensitized areas is tested directly twenty-four to forty-eight hours later with the food protein to which the donor reacts. If a skin reaction ensues at the prepared site the indication is that the donor's serum does contain circulating antibodies for specific foods, and we are then prepared to proceed with our experiment.

Twenty-four to forty-eight hours after the direct skin test, the recipient ingests the modified or processed foodstuff under investigation. If no reaction ensues in the passively sensitized areas, the recipient then ingests the food in its native form twenty-four to forty-eight hours later. The absence of a reaction from the ingestion of food in modified form and the subsequent presence of a reaction following the ingestion of the same food in native form objectively demonstrates that some change has occurred in the allergenicity of the foodstuff from the heat treatment or other processing to which it has been subjected, or that it did not pass

through the intestinal wall. The positive reaction usually occurs within fifteen to thirty minutes or later, and persists for several hours.

If reactions are not obtained with the modified or the native form of

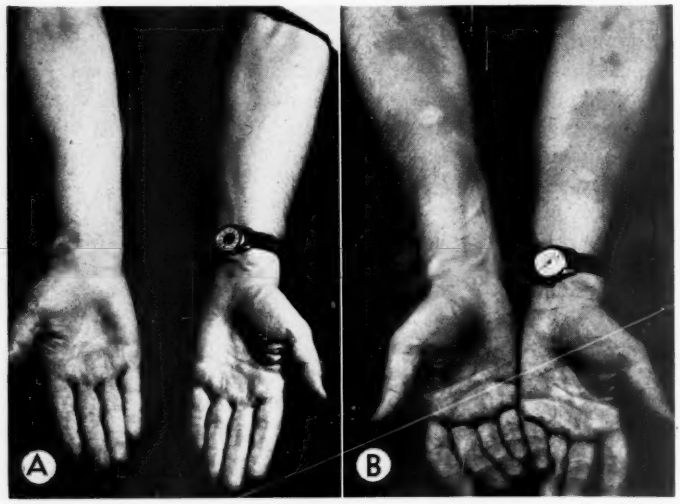

Fig. 1. The Dual Ingestion Passive Transfer Test with hard boiled (30 minutes) egg and raw egg white. Recipient C. C. W.:

A. Picture taken two hours after ingestion of three hard boiled egg whites—no reaction at sensitized sites of the forearms.

B. Picture taken one and one-half hours after ingestion of two raw egg whites several hours after the above negative reactions. Reactions occurred fifteen minutes after ingestion in five sites. The upper left-hand site was exhausted because of a previous positive direct skin test.

the foodstuff after ingestion, despite a positive direct passive transfer test, several assumptions can be made:

1. That the native form did not pass the intestinal wall at that particular time in that particular recipient. We have found in our experiments that in certain instances the test must be repeated at some other time.

2. If a number of recipients do not react and the majority do react to the native form, the test is valid. A large number of recipients is necessary. The question of varying degrees of intestinal permeability is thus demonstrated.

3. If negative reactions are obtained on all of a large sampling of recipients we must assume that:

(a) The titer of the serum is too low, or

(b) The food allergen is high in molecular weight and does not pass the intestinal wall, or

(c) The food ingested is too weak an antigen. We were confronted with this problem in our orange juice studies.

Since we are able to demonstrate in measurable form, under controllable conditions, the phenomenon, which occurs when ingested materials react, or fail to react, with the sessile antibodies resident in passively sensitized

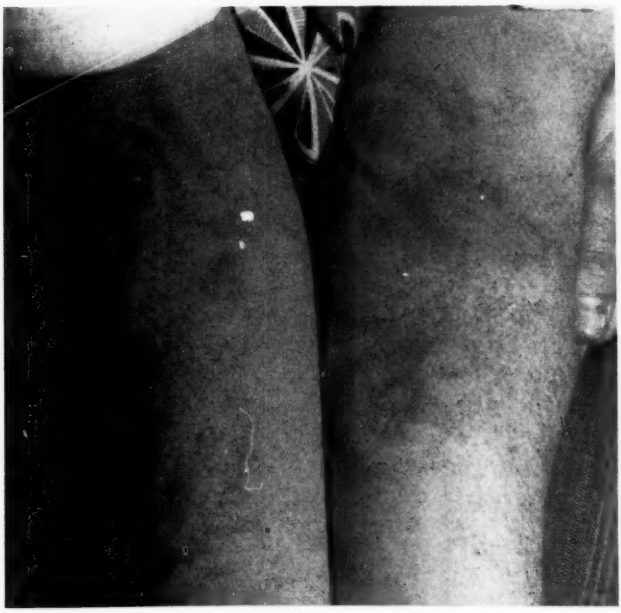

Fig. 2. The Dual Ingestion Passive Transfer Test with boiled codfish. Recipient M. C.:
This figure represents a positive reaction after the ingestion of boiled codfish in two previously sensitized sites on the left arm.
The previous day no reaction ensued after the ingestion of two ounces of cod liver oil.

sites in normal recipients, we believe we have devised an objective method for studying the influence of various modifications of proteins upon their allergenicity and passage through the intestinal membranes.

Our preliminary experiments have yielded several interesting findings.

Egg proteins subjected to moist heat appear to lose some allergenicity of the albumin and globulin fractions, but the ovomucoid fraction is not entirely affected in this respect. Hence, the individual sensitive only to the former fractions will be able to tolerate a hard boiled egg, whereas the individual sensitive to ovomucoid may not (Fig. 1).

Fish proteins, on the other hand, appear to remain highly allergenic in spite of subjection to moist heat.

Cod liver oil was shown to have no allergenicity, in relation to codfish hypersensitivity (Fig. 2).

Peanut oil was shown to be non-allergenic, whereas peanuts are highly allergenic (Fig. 3).

Orange juice, devoid of seed protein and peel oil, is hypoallergenic and non-irritating.

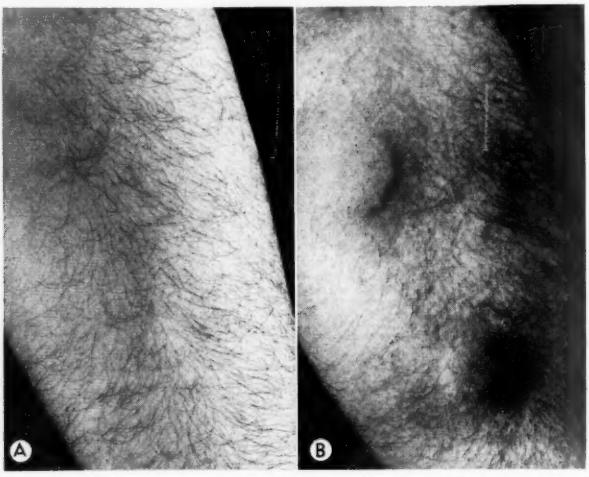

Fig. 3. The Dual Ingestion Passive Transfer Test with peanut oil and peanut. Recipient B. R.:
A. No reaction after ingestion of four ounces of peanut oil in two passively sensitized sites.
B. Following day—reaction after ingestion of one teaspoonful of ground peanut in same sites that did not previously react to the peanut oil ingestion.

We do not claim that we have devised a completely new method, but have used certain well known procedures in a novel way to fortify a concept. There is, after all, little new that anyone can claim. Interestingly enough, after our studies were completed, a review of the literature revealed that Bernton[1] had used a procedure similar to ours in testing allergy to corn oil, and I am certain that many others have used similar procedures in trial diet studies without reporting them. What we wish to emphasize here is that this method which we have labeled *dual ingestion passive transfer test* should be adopted specifically for the study of the allergenicity of foodstuffs, and should supplant the doubtful trial feeding methods.

CONCLUSIONS

Demonstration, under controlled conditions, of the phenomenon that ingested foodstuffs react or fail to react in passively sensitized areas in non-allergenic human subjects offers an objective procedure for the study of the allergenicity of foods in man.

We believe the *dual ingestion passive transfer test* described is a new approach to the study in man of the effect of various modifications and processing of food proteins on their allergenicity and ease of passage through the intestinal wall.

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The ANNALS is not just another journal, but the official organ of a liberal College. One of its functions, besides the educational material it contains, is to keep its members informed of the important events which are transpiring from time to time in the College. If you would do this, much correspondence would be eliminated answering questions which have been previously published in the ANNALS.

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ALLERGENICITY OF MODIFIED AND PROCESSED FOODSTUFFS

II. Orange: Anaphylactogenic Properties of a Specially Prepared Infant Orange Juice Determined in the Guinea Pig

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WE INVESTIGATED the anaphylactogenic properties of a specially prepared infant orange juice which is purported to contain no orange seed protein or orange peel oil.* Hence, we attempted in this study to determine the anaphylactogenicity of this single modified form of orange juice. Future studies will be made with other forms of processed orange juice.

ANAPHYLAXIS PROCEDURES USED

In reviewing the literature we were unable to find any work that has been done in the lower animal on the anaphylactogenic properties of orange juice.

Normal guinea pigs weighing approximately 250 grams, and which had never been fed oranges, were used for the anaphylaxis studies.**

After many preliminary experiments we decided upon the routes and dosage schedules that would give the highest order of anaphylactogenicity that might be present in the various substances tested. With such a procedure we believed that relatively comparable data could be obtained.

The anaphylaxis tests comprised sensitization and shock procedures, with an intervening incubation period of three to four weeks. Sensitizing doses were generally given intraperitoneally, unless otherwise indicated. Shock injections were given by the intravenous route.

An important facet of our work was the use of the *double shock technique*. We have employed this method in previous studies.[1,2,3] In this procedure a second challenging dose of the material used for sensitization is given an hour or more after a negative reaction is obtained with a first challenging injection of the modified form of the substance under investigation. The purpose is to determine whether the animal is sensitive to the original material. This we believe is a sound method to determine anaphylactogenicity of modified forms of proteins. If a negative shock reaction is obtained with a related or modified form, one is not justified in con-

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*According to the manufacturers, this juice is filtered by a special method and contains no orange seed protein and no orange peel oil. It is especially designed for infants and children. This canned orange juice was generously supplied to us by the Bib Corporation.
**Supplied by Carworth Farms of New City, N. Y.

cluding that it does not possess allergenicity. Such a conclusion can only be valid if it can be shown that the animal was originally sensitive to the unmodified substance. This is the purpose of the *double shock method,* since the first shock dose utilizes the modified form, and the second shock dose the homologous form of the material being tested and with which the animal was originally sensitized. Hence, we believe that the experiments detailed in this paper are validated by our use of the control shock technique.

The absence of primary reactions with the sensitizing dose and various gradations of positive reactions with the shock dose are evidence that the materials used are of good antigenic quality. Unless an antigenic material fulfills these criteria, one cannot accept the results obtained. For example if all the animals tested died uniformly, this would seem to indicate that the material has primary toxicity and is not solely anaphylactogenic.

Another point to consider is the number of animals used. One can readily see that if few animals are employed chance may play a role and it is possible that three or four animals consecutively may react negatively. If, however, ten or more animals are employed, the element of chance is reduced and a sounder evaluation of the situation is possible. It will be noted from our data that all materials were tested in an adequate sampling of animals.

We did not embark on these experiments until many preliminary tests were done in each group to determine optimum routes and dosage. In general, all sensitizing doses were three times larger than the shock doses. Preliminary tests showed that the intraperitoneal route was not regularly effective, and all shock injections were therefore given by the intravenous route.

Smaller doses of the orange peel oil were used because of its irritating quality.

We were quite satisfied that only with such rigorous standards would we be able to demonstrate to what extent the orange juice under investigation, which contains only 0.045 per cent protein nitrogen, is anaphylactogenic. The cross relationships of the juice, the seed and the peel oil were investigated to determine if possible the factors responsible for the allergenicity of orange juice.

ANAPHYLACTOGENICITY OF ORANGE SEED PROTEIN

In the study of the protein derived from orange seed there is evidence that the anaphylactogenicity is of a high order.*

There was unmistakable evidence of anaphylaxis when challenging doses of orange seed protein, in dilutions of 1:1000, 1:500 and 1:100,

*This protein extract was generously prepared for us by Seymour L. Shapiro, Director of Biological Laboratories of the Arlington Chemical Company, U. S. Vitamin Corporation (now the Arlington Allergy Division of the Hollister-Stier Corporation). The extract in 1:100 dilution contained 0.075 per cent protein nitrogen.

TABLE I. ANAPHYLACTOGENIC PROPERTIES OF ORANGE SEED PROTEIN (OSP)

Number of Animals	Sensitivity Dose OSP	Shock Dose with Dilutions OSP	Result	Control Shock Dose OSP	Result
3	1 cc Ip.* 1:100	0.3 cc Iv.** 1:100,000	0 0 0	0.3 cc Iv. 1:100	++++ 0 ++++
3	1 cc Ip.* 1:100	0.3 cc Iv. 1:10,000	0 0 0	0.3 cc Iv. 1:100	++++ ++ ++++
10	1 cc Ip.* 1:100	0.3 cc Iv. 1:1000	0 0 0 0 + +++ ++ + 0 ++	0.3 cc Iv. 1:100	0 ++++ 0 ++++ ++ ++++ +++ +++ 0 ++++
2	1 cc Ip.* 1:100	0.3 cc Iv. 1:500	++ ++++		
21	1 cc Ip.* 1:100	0.3 cc Iv. 1:100	0 0 0 ++++ ++++ ++++ ++ 0 ++++ ++++ ++++ 0 ++ ++++ +++ +++ 0 ++++ 0 0 0		

*Ip.—Intraperitoneal route.
**Iv.—Intravenous route.
++++ Anaphylactic death.
+++, ++, + Anaphylactic shock with recovery.

were given intravenously to animals sensitized with orange seed protein (Table I.).

ANAPHYLACTOGENICITY OF BIB ORANGE JUICE

Bib orange juice gives evidence of anaphylactogenicity only in the concentrated form.** However, no shock reactions were observed when dilutions of 1:1000, 1:500 or 1:100 were used (Table II). These negative results are noteworthy in view of the reactions observed with similar dilu-

TABLE II. ANAPHYLACTOGENIC PROPERTIES OF BIB ORANGE JUICE (BOJ)

Number of Animals	Sensitivity Dose Concentrated BOJ	Shock Dose with Dilutions BOJ	Result	Control Shock Dose Concentrated BOJ	Result
5	1 cc Ip.	0.3 cc Iv. 1:100,000	0 0 0 0 0	0.3 cc Iv.	++++ + +++ 0 0
5	1 cc Ip.	0.3 cc Iv. 1:1000	0 0 0 0 0	0.3 cc Iv.	++ + ++++ 0 0
20	1 cc Ip.	0.3 cc Iv. 1:100	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	0.3 cc Iv.	0 0 + ++++ ++ ++++ + ++++ +++ +++ ++++ +++ 0 0 0 0 0 ++++ 0 0
5	5 cc Ip.	0.3 cc Ip. 1:500	0 0 0 0 0	0.3 cc Iv.	++++ ++++ ++++ ++ 0
10	5 cc Ip.	1 cc Ip. conc.	0 0 0 0 0 0 0 0 0 0	0.3 cc Iv.	++++ ++++ ++++ ++ 0 ++++ 0 ++ + ++++

tions of orange seed protein. It seems reasonable to assume, therefore, that although the Bib juice has anaphylactogenic properties it is much weaker anaphylactogenically than the extract from orange seed. The anaphylactogenicity of concentrated Bib orange juice is about the same as a 1:100 dilution of the seed extract.

TABLE III.
ABSENCE OF ORANGE SEED PROTEIN (OSP) IN BIB ORANGE JUICE (BOJ)

Number of Animals	Sensitivity Dose OSP 1:100	Shock Dose BOJ Concentrated	Result	Control Shock Dose OSP 1:100	Result
18	1 cc Ip.	0.3 cc Iv.	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	0.3 cc Iv.	++++ ++++ 0 ++++ ++++ ++++ ++ 0 ++++ ++++ ++++ 0 ++++ ++++ +++ ++ ++++ 0

Number of Animals	Sensitivity Dose BOJ Concentrated	Shock Dose OSP 1:100	Result	Control Shock Dose BOJ Concentrated	Result
13	1 cc Ip.	0.3 cc Iv.	0 0 0 0 0 0 0 0 0 0 0 0 0	0.3 cc Iv.	0 + ++++ 0 ++++ 0 0 ++++ ++++ 0 0 + 0
5	5 cc Ip.	0.3 cc Iv.	0 0 0 0 0	0.3 cc Iv.	++++ 0 ++ + ++++

ABSENCE OF ORANGE SEED PROTEIN IN BIB ORANGE JUICE

We attempted to determine whether any seed protein was present in the Bib juice. In Table III is listed a series of experiments in which animals were given a sensitizing dose of concentrated Bib juice and challenged with a 1:100 dilution of orange seed protein, and conversely given a sensi-

**This concentrated juice contains 0.045 per cent protein nitrogen.

TABLE IV. PRIMARY TOXICITY OF ORANGE PEEL OIL (OPO)

Animal Number	Primary Injection	Result
102	0.1 cc OPO Iv. (concentrated)	Ran in circles with severe dyspnea and death in approximately ten minutes. Necropsy: Hemorrhagic distended lungs with scattering of multiple emboli and infarcts.
104	0.3 cc concentrated OPO Iv.	Immediate death—no signs typical of anaphylaxis—absence of dyspnea—apnea and collapse. Necropsy: distended lungs, petechial hemorrhages and emboli.
143	0.3 cc concentrated OPO Iv.	Extreme irritability, frantic running around, convulsive movements and recovery.
144	0.3 cc concentrated OPO Iv.	Immediate death—no signs typical of anaphylaxis. Necropsy: lungs hemorrhagic and embolic.
145	0.3 cc concentrated OPO Iv.	Extreme irritability, frantic running around, convulsive movements and recovery.
146	0.3 cc concentrated OPO Iv.	Ran in circles with severe dyspnea. Death in approximately ten minutes. Necropsy: hemorrhagic lungs and scattering of multiple emboli and infarcts.
147	0.3 cc concentrated OPO Iv.	Ran in circles with severe dyspnea. Death in approximately ten minutes. Necropsy: hemorrhagic lungs and scattering of multiple emboli and infarcts.

tizing dose of orange seed protein and challenged with Bib. There were no cross reactions in either instance. This suggests that Bib orange juice does not contain orange seed protein in amounts detectable by the method employed.

By the double shock control we showed anaphylactic reactivity to the homologous sensitizing proteins. This suggests that the proteins in the seed and in the juice have independent antigenicities.

PRIMARY TOXICITY OF ORANGE PEEL OIL

From our own clinical experience and that of others we were cognizant of the fact that orange peel oil has primary toxicity. This was demonstrated experimentally in a series of 7 normal animals which were given 0.1 to 0.3 cc of concentrated orange peel oil intravenously.*

In Table IV it will be noted that two animals died immediately after the intravenous injection of concentrated orange peel oil. Necropsy showed the lungs to be distended, and having a wide distribution of multiple emboli. The animals were not dyspneic before death. Death occurred so rapidly that only apnea and extreme collapse were present.

Three animals showed extreme irritability, marked dyspnea and convulsions, and died within ten minutes. They presented markedly hemorrhagic lungs with a scattering of multiple emboli and infarcts.

*This oil was expressed from the oranges used in the manufacture of Bib orange juice and supplied to us by the Bib Corporation.

TABLE V. ANAPHYLAXIS EXPERIMENTS WITH ORANGE PEEL OIL (OPO)

Number of Animals	Sensitivity Dose OPO	Shock Dose OPO	Result
5	1 cc subcut. 1:500	0.3 cc Iv. 1:250	0
5	1 cc subcut. 1:500	0.3 cc Iv. 1:100	0
5	0.3 cc Ip. 1:500	0.3 cc Iv. 1:100	0
5	1 cc Ip. 1:250	0.3 cc Iv. 1:100	0
5	1 cc Ip. 1:250	0.3 cc Iv. 1:250	0

TABLE VI. ABSENCE OF CROSS ANAPHYLAXIS BETWEEN ORANGE PEEL OIL (OPO) SEED (OSP) AND JUICE (BOJ)

Number of Animals	Sensitivity Dose	Shock Dose	Results
5	OPO 1:500 1 cc subcut.	OSP 1:100 0.3 cc Iv.	0
5	OPO 1:500 1 cc subcut.	BOJ conc. 0.3 cc Iv.	0

The two animals that recovered demonstrated extreme irritability—running around frantically, with convulsive movements.

Animals injected intraperitoneally with the concentrated material, and even with a 1:250 dilution, as a rule showed a transient irritability. The material seemed to have a burning effect.

NON-ANAPHYLACTOGENICITY OF ORANGE PEEL OIL

Since we proposed to do anaphylaxis experiments with this oil, and it could not be used in concentrated form, it was mixed in a buffered saline solution in dilutions of 1:100, 1:250 and 1:500. These dilutions did not prove primarily toxic when injected intravenously in doses of 0.3 cc. into 32 normal control animals.

From Table V it will be noted that orange peel oil is not anaphylactogenic in the dilutions employed.

ABSENCE OF ORANGE SEED PROTEIN AND ORANGE JUICE PROTEIN IN ORANGE PEEL OIL

Anaphylaxis tests with orange peel oil as a sensitizing dose (Table VI) did not show any cross reaction with the orange seed protein or the Bib orange juice. Such a procedure may seem unnecessary in the light of the experiments detailed in Table V, but these experiments were carried out to further fortify the conclusion arrived at with respect to the non-anaphylactogenicity of the oil.

CONCLUSIONS

1. The antigens contained in orange seed protein and those in orange juice appear to have independent antigenic specificities.

2. Orange peel oil was demonstrated to be non-anaphylactogenic. It does, however, possess primary toxic properties.

3. Concentrated Bib orange juice was anaphylactogenic when it was used as the sensitizing and shock agent. This anaphylactogenicity is of a low order. Employed in a dilution of 1:100 there was no evidence of anaphylactogenicity, whereas orange seed protein in dilutions of 1:1000 was shown to have a high degree of anaphylactogenicity.

4. The juice under investigation was shown to be devoid of seed protein and peel oil. Within the limits of our experiments we believe it reasonable to conclude that it is hypoallergenic and non-toxic.

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In a time of tension and cynicism it is well to be reminded of the inherent goodness of people, to call attention to their constant voluntary efforts to make life a little better for the men and women in the armed forces, for hospitalized veterans, for disaster sufferers, and for those in need in other lands.

Although the heart and hands of the Red Cross are provided by hundreds of thousands of volunteers, money is also needed to collect blood; to provide financial assistance for servicemen, veterans, and their dependents; to furnish emergency aid and rehabilitation to disaster victims—services that can be provided only through the voluntary financial support of millions of Americans.

Every March Red Cross volunteers turn to their neighbors and ask help in answering the call of those in need. Let us respond generously to this appeal so that we can answer the call of humanity through our Red Cross.

ALLERGENICITY OF MODIFIED AND PROCESSED FOODSTUFFS

III. Peanut: Non-allergenicity of Peanut Oil

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THIS STUDY seeks to provide objective data on the antigenicity of peanut oil. The tolerance for such an oil by individuals hypersensitive to the foodstuffs from which it has been derived has been a matter of dispute.[1,2,4,5] The reported results of direct tests with such oils and reactions to oral ingestion by the allergic subject have not been entirely satisfactory. This investigation was undertaken using a technique which we believe is objective, eliminating any subjective interpretation of the reactions to the ingested material on the part of the patient, or evaluation of the reactions on the part of the observer. This technique we termed Dual Ingestion Passive Transfer Test and is described fully in paper I of this series.[7] Anaphylactic tests in the guinea pig were also employed.

ALLERGENICITY OF PEANUT

A. Passive Transfer Test.—In order to test the potency of the serum and the antigenic materials used, direct passive transfer tests by the Prausnitz-Küstner (PK) method were done with an anti-peanut human serum (MW) on a total of twenty-two non-allergic children. Twelve were tested with a 1:100 peanut antigen dilution, and ten with a 1:1000 dilution. Peanut antigen, 0.02 cc, was injected intradermally into skin sites which were passively sensitized twenty-four hours previously with 0.05 cc anti-peanut human serum. All showed a positive transfer as listed in Table I. The anti-peanut serum was titrated and found to be highly potent in a 1:40 dilution and moderately so in 1:80. The recipients in these tests ranged from four to twelve years of age and were all convalescent tuberculous patients free from any active illness.*

B. Ingestion Passive Transfer Test.—In order to provide a comparative study of the antigenicity of peanut oil by ingestion, sixty-nine recipients were passively sensitized (PK method) with the serum in the preceding manner, then twenty-four hours later were given one teaspoonful of ground

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Dr. Collins-Williams was formerly associated with the New York Medical College.

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*Pediatric Division of Sea View Hospital.

TABLE I. PRAUSNITZ-KUSTNER (PK) REACTIONS TO PEANUT IN TWENTY-TWO NON-ALLERGIC CHILDREN*

No.	Reaction to Peanut 1:100 Dilution				No.	Reaction to Peanut 1:1000 Dilution			
	Sensitized Site		Non-sensitized Site			Sensitized Site		Non-sensitized Site	
	Erythema	Wheal	Erythema	Wheal		Erythema	Wheal	Erythema	Wheal
1	1½ in.	1¼ in.	½ in.	0	13	1½ in.	½ in.	⅛ in.	0
2	1¼ in.	¾ in.	0	0	14	2 in.	⅝ in.	⅛ in.	0
3	2 in.	1 in.	0	0	15	1¾ in.	¾ in.	¼ in.	0
4	1½ in.	¾ in.	½ in.	0	16	¾ in.	¼ in.	⅛ in.	0
5	1½ in.	½ in.	½ in.	0	17	2 in.	½ in.	¼ in.	0
6	1½ in.	½ in.	0	0	18	1¾ in.	⅜ in.	⅛ in.	0
7	¾ in.	¼ in.	½ in.	0	19	1½ in.	¾ in.	⅛ in.	0
8	1½ in.	½ in.	¼ in.	0	20	2 in.	1¼ in.	¼ in.	0
9	2 in.	1¼ in.	¼ in.	0	21	1¼ in.	¾ in.	0	0
10	1¾ in.	1 in.	½ in.	¼ in.	22	2½ in.	1¼ in.	0	0
11	1¾ in.	1 in.	½ in.	¼ in.					
12	1 in.	½ in.	½ in.	0					

*Peanut antigen 0.02 cc injected intradermally into skin sites passively sensitized with 0.05 cc intradermally of human anti-peanut serum twenty-four hours previouslv.

TABLE II. INGESTION PASSIVE TRANSFER TEST WITH PEANUT IN NON-ALLERGIC CHILDREN

Number of Recipients Tested	Number of Positive Reactors*	Number of Negative Reactors	Percentage of Positive Reactors
69	56	13	81%

*Reactions noted, after ingestion of ground peanut, at skin sites passively sensitized twenty-four hours previously with human anti-peanut antigen by PK method.

peanut by mouth, followed by a glass of water. They were observed for several hours and the reactions are noted and listed in Table II. It will be seen that 81 per cent of these recipients gave positive reactions.

Even though 100 per cent of the recipients reacted positively by direct passive transfer test in the twenty-two cases listed in Table I, it is generally conceded that about 85 per cent of normal recipients accept direct passive transfer. Therefore the high figure (81 per cent) that we obtained by the Ingestion Passive Transfer Test is indicative of the high potency of this serum and the high degree of intestinal permeability of the subjects tested. This emphasizes the reliability of the control that is thus established in the evaluation of the antigenicity of peanut oil.

NON-ALLERGENICITY OF REFINED PEANUT OIL

Dual Ingestion Passive Transfer Test.—A standard brand of edible peanut oil was given to eight non-allergic volunteer physicians previously sensitized on the forearms with the anti-peanut serum. As noted in Table

TABLE III. DUAL INGESTION PASSIVE TRANSFER TEST WITH PEANUT OIL AND GROUND PEANUT IN ADULT RECIPIENTS*

Case	Ingestion of Peanut Oil	Period of Observation	Reaction at Sensitive Site	Control Ingestion Ground Peanut	Reaction at Sensitive Site	Time of Reaction
C.C.W.	2 oz.	3 hrs.	0	1 oz.	+	20 minutes
C.C.W.	3 oz.	20 hrs.	0	1 teasp.	+**	40 minutes
B.R.	3 oz.	20 hrs.	0	1 teasp.	+	15 minutes
W.B.	2 oz.	¾ hr.	0	1½ teasp.	+	20 minutes
R.P.	2½ oz.	1 hr.	0	1½ teasp.	+	35 minutes
S.U.	2½ oz.	2 hrs.	0	1½ teasp.	+	55 minutes
B.S.	4 oz.	1 hr.	0	1½ teasp.	+	45 minutes
M.L.	4 oz.	1 hr.	0	1½ teasp.	+	35 minutes
D.Y.	½ oz.	¾ hr.	0	1½ teasp.	0	0
D.Y.	1 oz.	1½ hrs.	0	1½ teasp.	+**	35 minutes

*Individuals were passively sensitized to peanut and the following day ingested peanut oil. After noting the negative reactions all the recipients ingested ground peanut.
**Repeated test the following week.

III, no reactions were elicited in any sensitized area following ingestion of amounts of oil ranging from one-half ounce to four ounces. These were observed from three-fourths to twenty hours.

Proof by the dual ingestion test that the sites were effectively sensitized was afforded by the ingestion of ground peanut given after the period of observation noted above. In seven instances reactions were obtained after the ingestion of from 1 dram to 1 ounce of ground peanut. In the eighth case (DY) no reaction occurred at first trial test. However, when peanuts were again ingested one week later, positive reactions resulted within thirty-five minutes.

It is interesting to note that in this one instance intestinal permeability to peanut protein was lacking at the first trial, whereas when the test was repeated the following week, passage was evident. This indicates the need for doing this experiment with multiple subjects and at different times when a negative passage is obtained.

Figures 1 and 2 are illustrated examples of the objective demonstration by our Dual Ingestion Passive Transfer Test that a modified foodstuff has lost the allergenicity present in the unmodified form.

It was thus demonstrated that peanut oil taken in large amounts failed to elicit reactions in the sites of the subjects passively sensitized with peanut antibody. However, the ingestion of whole ground peanut gave positive reactions in sensitized sites of all the individuals who gave negative reactions to the oil. Insofar as the intestinal tract in these individuals is shown to be normally permeable to peanut protein we must assume that the oil is non-allergenic or that it does not pass the intact intestinal wall and therefore cannot act as an allergen.

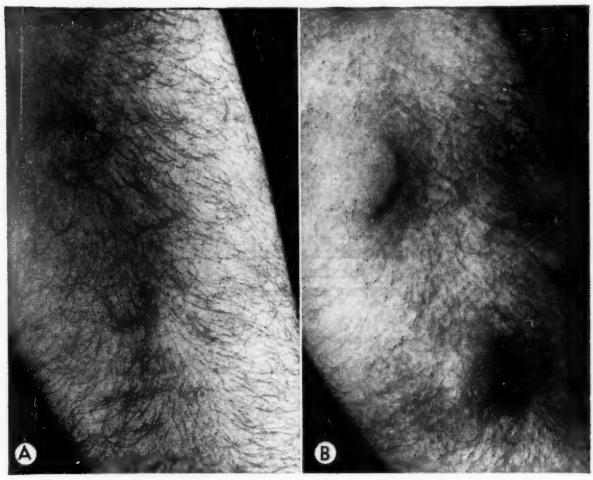

Fig. 1. The Dual Ingestion Passive Transfer Test with Peanut Oil and Peanut. Recipient B. R.: *(A)* No reaction after ingestion of four ounces of peanut oil in two passively sensitized sites. *(B)* Following day—reaction after ingestion of 1 teaspoonful of ground peanut in same sites that did not previously react to the peanut oil ingestion.

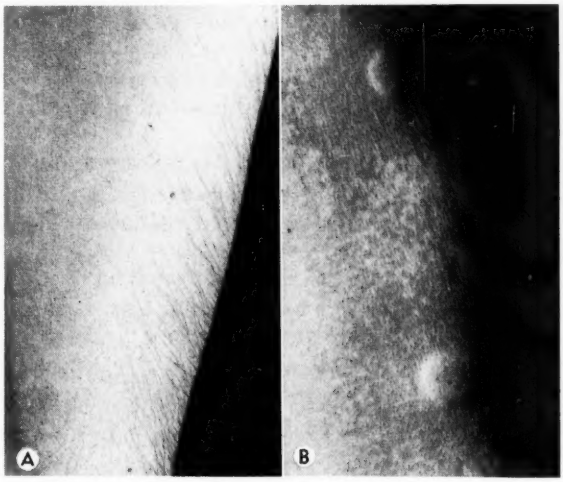

Fig. 2. The Dual Ingestion Passive Transfer Test with peanut oil and peanut. Recipient C. C. W.: *(A)* No reaction after 3 ounces of peanut oil in 2 passively sensitized sites. *(B)* Following day—reaction after 1 teaspoonful of ground peanut in same sites that did not react previously to the peanut oil ingestion.

TABLE IV. DUAL INGESTION TEST SHOWING NON-ALLERGENICITY OF BREMIL TO PEANUT*

Number Children Tested	Ingestion of Bremil	Period of Observation	Reaction at Sensitized Site	Control Ingestion Ground Peanut	Reaction at Sensitized Site		Percentage Positive to Peanut
					Positive	Negative	
25	6 oz.	3½ hrs.	0	1 teasp.	17 (15-30 minutes)	8	68%

*Twenty-five children passively sensitized to peanut protein all reacted negatively to the peanut-oil-containing Bremil. With the control ingestion of ground peanut 68 percent reacted positively at the passively sensitized sites.

NON-ALLERGENICITY OF A COMPOSITE FOODSTUFF CONTAINING PEANUT OIL

We were unable to repeat this experiment with the children because they did not voluntarily want to consume the oil as such. We therefore resorted to a more palatable form of peanut oil preparation.

The antigenicity of a commonly used infant food containing peanut oil (Bremil)* as one of its ingredients was chosen for investigation. Twenty-five non-allergic children previously sensitized at local sites with this anti-peanut serum drank 6 ounces of reconstituted Bremil. No reactions ensued in the following three and one-half hour period.

When given 1 teaspoonful of ground peanut by mouth following this three and one-half hour period of observation, reactions were noted in seventeen instances (68 per cent of the subjects tested) within fifteen to thirty minutes (Table IV).

It was thus demonstrated that this food product, taken in the amount usually ingested in an average instance, failed to elicit reactions in the sensitized skin sites.

The donor (MW), who reacts with urticaria upon touching peanuts and who gets generalized giant urticaria and asthma from ingestion, consumed 1 ounce of peanut oil and/or 6 ounces of Bremil each day for two weeks without any reaction.

NON-ALLERGENICITY OF AN ANTIBIOTIC DISPENSED IN A PEANUT OIL MENSTRUUM

Reactions have been described following the injection of procaine penicillin in peanut oil menstruum. Some have been attributed to reactions to the peanut oil. Whether this menstruum could produce reactions in anti-peanut sensitized sites was investigated in twenty children. These individuals received penicillin injections for therapeutic reasons.

Prior to the injection of this penicillin preparation, passively sensitized sites were prepared in the forearm with the anti-peanut serum. The follow-

*This foodstuff contains a mixture of 26.7 per cent oils (peanut, coconut and palm) and was kindly supplied by Dr. Julius F. Mueller, Borden Company.

TABLE V. ANIMALS SENSITIZED WITH PEANUT PROTEIN (PP) AND CHALLENGED WITH REFINED PEANUT OIL (RPO)

Number of Animals	Sensitizer	Shock Injection	Result	Control Shock Injection	Result
10	1 cc PP (1:100) Ip.	3 cc RPO Ip.	0	0.05 cc PP Iv.	++++
	1 cc PP (1:100) Ip.	3 cc RPO Ip.	0	0.05 cc PP Iv.	++++
	1 cc PP (1:100) Ip.	3 cc RPO Ip.	0	0.1 cc PP Iv.	++++
	1 cc PP (1:100) Ip.	3 cc RPO Ip.	0	0.05 cc PP Iv.	++++
	1 cc PP (1:100) Ip.	3 cc RPO Ip.	0	0.05 cc PP Iv.	++++
	1 cc PP (1:100) Ip.	3 cc RPO Ip.	0	0.05 cc PP Iv.	++
	1 cc PP (1:100) Ip.	3 cc RPO Ip.	0	0.05 cc PP Iv.	+++
	1 cc PP (1:100) Ip.	3 cc RPO Ip.	0	0.1 cc PP Iv.	+++
	1 cc PP (1:100) Ip.	3 cc RPO Ip.	0	0.1 cc PP Iv.	++
	1 cc PP (1:100) Ip.	3 cc RPO Ip.	0	0.05 cc Iv.	++++

++++—anaphylactic death with typical ballooned lungs.
+++. ++—varying degrees of anaphylaxis with recovery.
Ip.—intraperitoneal injection.
Iv.—intravenous injection.

ing day an injection of 1 cc penicillin in peanut oil* was given into the gluteal muscle. No reactions in any sensitized skin site occurred during ninety to 115 minutes.

The absence of any reaction led us to question whether peanut antigen injected parenterally could elicit reactions in the sensitized areas. Accordingly we injected 0.04 cc of 1:1000 peanut antigen** intradermally in non-sensitized sites into twelve children. No reactions occurred in the sensitized areas in any instance. Using the same dilution (1:1000), four children were given 0.04 cc intramuscularly. No reactions were noted.

Then two children were given 0.04 cc peanut antigen (1:100) intramuscularly. Within five minutes positive reactions occurred at the sensitized skin sites.

When this was repeated in ten children who were injected with 0.04 cc peanut 1:100, using the intradermal instead of the intramuscular route, positive reactions ensued in two instances within forty-five minutes.

This proved that if the peanut oil injected intramuscularly had contained at least as little as 0.04 cc of a 1:100 dilution of peanut antigen (0.16 per cent protein nitrogen), such a small amount would have been sufficient to produce a positive reaction in the sensitized sites. We must deduce that this small amount of antigen in a sensitized patient would be capable of reacting in a shock organ. It is apparent that this penicillin in peanut oil did not contain peanut antigen sufficient to elicit allergic reactions.

*Depo Penicillin, 300,000 units per cc (Upjohn), contains crystalline procaine penicillin G suspended in peanut oil.

**This antigen was prepared for us by Seymour L. Shapiro, Director of Biological Laboratories of the Arlington Chemical Company, U. S. Vitamin Corporation (now the Arlington Allergy Division of the Hollister-Stier Corporation). This peanut antigen is the same as that regularly used by allergists for diagnostic and therapeutic purposes. The antigen contained 0.016 per cent protein nitrogen in 1:1000 dilution and 0.16 per cent in 1:100 dilution.

TABLE VI. ANIMALS SENSITIZED WITH PEANUT PROTEIN (PP), CHALLENGED WITH BREMIL AND CONTROL SHOCKED WITH PEANUT PROTEIN

Number of Animals	Sensitizer	Shock Injection	Result	Control Shock Injection	Result	2nd Control Shock Injection	Result
10	1 cc PP Ip.	3 cc Ip. Bremil	0	1 cc PP Ip.	0	0.3 cc PP Iv.	+++
	1 cc PP Ip.	3 cc Ip. Bremil	0	1 cc PP Ip.	+	0.3 cc PP Iv.	++
	1 cc PP Ip.	3 cc Ip. Bremil	0	1 cc PP Ip.	0	0.3 cc PP Iv.	++++
	1 cc PP Ip.	3 cc Ip. Bremil	0	1 cc PP Ip.	+++	0.3 cc PP Iv.	++++
	1 cc PP Ip.	3 cc Ip. Bremil	0	1 cc PP Ip.	0	0.3 cc PP Iv.	++
	1 cc PP Ip.	3 cc Ip. Bremil	0	1 cc PP Ip.	++	0.3 cc PP Iv.	++++
	1 cc PP Ip.	3 cc Ip. Bremil	0	1 cc PP Ip.	+	0.3 cc PP Iv.	++
	1 cc PP Ip.	3 cc Ip. Bremil	0	1 cc PP Ip.	++	0.3 cc PP Iv.	++++
	1 cc PP Ip.	3 cc Ip. Bremil	0	1 cc PP Ip.	++	0.3 cc PP Iv.	+++
	1 cc PP Ip.	3 cc Ip. Bremil	0	1 cc PP Ip.	+	0.3 cc PP Iv.	++

ANAPHYLAXIS EXPERIMENTS IN THE GUINEA PIG SHOWING NON-ALLERGENICITY OF PEANUT OIL AND BREMIL*

Ten animals (Table V were injected intraperitoneally with 1 cc (1:100 dilution) of peanut protein. Three weeks later they were each challenged with 3 cc refined peanut oil. In no instance was there any anaphylactic response. Two hours later they were given a control shock dose with 0.05 or 0.1 cc peanut protein intravenously. This method is fully described in paper II of this series.[6] All the animals showed profound anaphylaxis and/or anaphylactic death. This is strong evidence that the refined peanut oil tested is non-anaphylactogenic.

Ten animals (Table VI) were similarly injected with 1 cc peanut protein intraperitoneally, and three weeks later challenged with 3 cc of reconstituted Bremil intraperitoneally. In no instance was any evidence of anaphylaxis noted. Two hours later these same animals were challenged by the control shock with 1 cc peanut protein intraperitoneally, to determine whether this intraperitoneal shock route would elicit anaphylaxis to the homologous sensitizing agent. Unmistakable evidence of anaphylaxis was demonstrated.

A second control shock test, done intravenously one hour later, showed that the animals were profoundly sensitized to peanut protein.

In both series of animals we have therefore demonstrated that there is no evidence of peanut protein antigenicity resident in a refined peanut oil or in the composite foodstuff containing peanut oil (Bremil).

These animal experiments corroborate the results of our Dual Ingestion Passive Transfer Test in man.

COMMENT

As was amply discussed in papers I and II of this series, we believe that the methods we used to determine allergenicity of an edible vegetable oil

*The animal experiments were done with the technical assistance of Helen Lee Aikman, B.A., and Joseph S. Thomas, B.S.

is devoid of the pitfalls used by previous investigators. This whole question has led to a storm of controversy which culminated, in the fall of 1947, in a public hearing in Washington, by the Federal Security Administration.[3]

Allergenic reactivity to an oil has been greatly exaggerated. Foreign proteins cause allergic manifestations and pure oils contain no protein. Confirmation of this can be obtained by inquiry of the Council on Pharmacy and Chemistry of the American Medical Association or the Food and Drug Administration. Additional evidence supporting the lack of sensitization from oil vehicles may be found in the studies of Romansky[8] and Thomas et al,[9] who used peanut oil preparations in the main for injectant purposes. Reports in the earlier literature of allergic manifestations date back to the days when traces of foreign protein were present in the commercial preparations.

Much evidence is now at hand that if the vegetable oil is of standard purity, whether in edible or injectable form, no allergic manifestations should accrue from its use.

The studies of Bernton, Loveless (who also quotes the experiences of Halpin and Cazort), and our own experiments herein reported should, we believe, dispel the notion that refined edible or injectant oil is an allergen.

CONCLUSION

Within the limits of our experiments, refined peanut oil was found entirely devoid of allergenic and anaphylactogenic properties. It therefore can be ingested or injected into peanut allergic individuals.

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SERUM LEVELS OF POTASSIUM, PHOSPHORUS AND SODIUM DURING THE EXUDATIVE PHASE OF INFANTILE ECZEMA

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THE hypothesis that allergy is associated with altered electrolyte metabolism seems to have many facets, discussions of which may be found scattered throughout the literature. We were prompted to observe the serum levels of potassium, phosphorus, and sodium in acute infantile eczema to determine whether changes reported to occur in asthma might be present in eczema.

Dees observed that the fasting mean serum potassium levels in children with asthma were significantly higher than the mean serum potassium levels of control patients. Ruskin noted this to be questionably true for all allergic states. Donovan and Harsh found that the serum potassium was slightly higher in the asthmatic child than in the nonallergic child. They also found that the serum potassium concentration of the asthmatic child on an increased sodium diet was slightly higher than it was on an increased potassium diet. Cooke and Stoesser reported that disturbances in electrolyte metabolism could alter episodes of asthma; they found that following artificial fever therapy there were long remissions of symptoms in asthmatic patients when the patients were placed on a low sodium chloride diet, but there were no remissions when salt was unrestricted. When asthmatic patients were placed on a low salt diet, increased water intake and given Pitressin, the asthma ceased although weight gain was up 2 to 5 per cent. When they were given sodium chloride, attacks recurred. Stoesser and Booth observed that children with intractable asthma experienced notable clinical benefit from artificial fever therapy, ingestion of potassium chloride, or low sodium chloride diets.

Bloom, following studies of acute hay fever treated with potassium salts, noted striking benefits and postulated a "fundamental electrolyte disturbance in allergy associated with some endocrine (possibly adrenal) dysfunction." During infancy, the skin response to mechanical stimulation is at its maximum, as found in quantitative studies by Smith, Baine and Hallan. Urbach found a higher water content in the skin of eczematous babies, even in areas distant from the lesions. The McClure-Aldrich test consisting of an intradermal wheal shows, in this group, that the disappearance rate is unusually rapid, which suggests an increased water and/or sodium chloride content.

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SELECTION OF PATIENTS

Since acute eczema is characteristically seen during the first two years of life, all of our patients were chosen from this age group. Children under two years of age were selected also because of the following nonspecific factors: (1) eczema is known to occur predominantly in the acute form during the first year, tending to diminish after the second year; (2) the infant skin during this period is known to have a higher content of water and sodium chloride and a lower sodium to potassium ratio. This latter characteristic also tends to disappear with growth and is associated with maturing of the epidermis.

Since many factors may influence serum sodium, potassium, and phosphorus levels, the patients were selected from out-patients and patients on their first twenty-four hours of hospitalization. They were not on any diet which would increase serum potassium, they were not apparently dehydrated or starved, and they were free from diarrhea and fever. Since there may be some diurnal fluctuation in serum potassium levels associated with the urinary output, all blood was drawn during the day.

METHODS

The flame photometer was used for all serum potassium determinations and care was taken to use autoclaved dry syringes to prevent hemolysis of red cells. The glass test tubes used for the collection of blood had an insignificant amount of free potassium present and the blood was centrifuged within an hour after being drawn.

RESULTS

Serum potassium and sodium levels were determined on twenty-one consecutive cases of acute exudative infantile eczema. The serum potassium was elevated in proportion to the total area of exudation and to the acuteness of the process. The sodium levels were high to high normal. Serum phosphorus levels were determined on five of these patients and tended to fluctuate similarly to the serum potassium. Serum sodium and potassium determinations were obtained on ten control patients of the same age group and all determinations were normal. Total serum protein levels were determined on ten of our eczema patients and were normal. On one patient[18] when the skin had almost returned to normal and potassium and phosphorus levels were almost back to normal, with the addition of a food which caused a sudden recrudescence of the eczema, the potassium and phosphorus levels were again found to be very high.

DISCUSSION

The causes of the altered electrolyte balance noted here may be several. Tissue changes where the cell is unable to hold potassium and phosphorus due to damage may account in part for this. But it seems unlikely that this is the entire cause since similar findings have been noted in other atopic

TABLE I.

Case No.	Age (in mos.)	Milleq./Lt. Serum Potassium	Mgms. % Serum Phosphorus	Milleq./Lt. Serum Sodium	Comment
1	under 12	6.24		141	0-† wet on face
2	under 12	5.86		142	†-†† face
3	under 12	5.44		146	††-††† face, buttocks, popliteal anticubital fossa regions
4		5.80		146	†-†† face
5	under 12	8.89		150	††† wet eczema over entire body surface. EKG showed evidence of hyperkalemia.
	6 wks. later	6.44		no sodium level	clearing nicely with diet and local treatment.
6	under 18	6.62		148	††-††† involving face, arms and shoulder (mod. wet)
7	under 12	7.03		138	†-†† face, neck and shoulder (mod. wet)
8	under 12	6.30		156	†† of face
9	under 12	5.27		144	†-†† of face
10	under 18	12.80		131	†††-†††† over entire body
	2 wks. later	12.80		146	unimproved. Patient moderately toxic in appearance
11	under 12	7.90		143	††-††† entire body
12		6.74		131	†† face and shoulders
13		7.45		138	††-††† face and shoulders
14		7.79		144	††† over entire body
15	17	5.2	5.4	142	†† on face
16	10	5.92	4.2	145	entire skin but only †-†† wet
17	3	3.60	5.4	154	†-†† on cheeks. Diarrhea 1 wk. prior to adm.
18	2½				
	(3/21)	6.33	6.2	158	†††† over body extremities and face.
	(3/28)	5.04	5.08		cleared with vioform.
	(4/1)	7.08	6.9	136	placed on oats day prior to blood specimen and worse.
	(4/5)	5.99			started clearing after removal of oats from diet, local treatment and mulsoy diet.
19	6				
	(3/7)	6.16	6.6	138	face, chest, shoulders, anticubital and popliteal fossa areas ††
	(3/12)		4.5		cleared with mulsoy and 3% coat tar ungt.
20	36	8.66		152	†††† over all body
21	48	7.52		135	††† over all body

Key
†—erythema with some slight excoriation.
††—erythema with some excoriation, oozing and crusting.
†††—erythema, edema and rather marked oozing and crusting.
††††—marked erythema edema and weeping with some crusting and lichenification.

diseases where there is minimal tissue breakdown. No balance studies were obtained on these patients so that we do not know the total intake or output of potassium, sodium, phosphorus, and nitrogen. It could be that eczema is a stress with an associated, so-called "adaptive alarm reaction" with subsequent potassium and phosphorus mobilization and loss with a tendency towards sodium retention. These electrolyte changes may reinforce the degree of severity of the allergic disease and this could explain the observation whereby nonspecific stresses tend to take their toll in causing exacerbations and prolongation of symptoms. One example is the patient with asthma who has a recurrence of symptoms with menstruation, or the asthmatic and eczema patient who, following an unpleasant family scene, has a sudden recrudescence of symptoms. (Similarly, Dr. Julia Baker, in Mexico City, while studying 1,000 unselected children noted that 509 had allergic symptoms. Mexico City has an altitude of 7,325 feet. Evidence is presented that many children with manifestations of allergy in the United States experience exacerbations when taken to Mexico City and many children without allergic symptoms at lower altitudes develop allergic disease in Mexico City.)

SUMMARY AND CONCLUSIONS

1. Twenty out of twenty-one consecutive cases of infantile eczema in the exudative phase had an elevation of the serum potassium. 2. The serum potassium was elevated in proportion to the total area of exudation and to the acuteness of the process. 3. Sixteen patients had an elevation of the serum sodium and four additional patients had a high normal serum sodium. 4. Serum phosphorus levels were determined on five of these patients and tended to fluctuate similarly to the serum potassium. 5. With improvement of the eczema the electrolyte levels tended to revert to normal. 6. It seems unlikely that tissue breakdown is the entire cause of these findings, since similar changes have been noted in other atopic disease where tissue destruction is at a minimum. 7. A suggestion is made that these electrolyte changes may represent potassium and phosphorus mobilization and loss with sodium retention and subsequent water-logging of the shock organ. 8. These electrolyte changes together with changes from other nonspecific stresses may have an additive effect in causing exacerbations and prolongation of symptoms.

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NEW ANTIBIOTIC

A new wide-range antibiotic, "Ilotycin" (Erythromycin, Lilly) is now available. The new drug is the result of more than five years of intensive research in the antibiotic field. Over 100,000 mold organisms were isolated from soil samples from all over the world and tested before the one producing "Ilotycin" was found.

Clinical evidence shows that "Ilotycin" is especially effective against Gram-positive infections which have become resistant to other commonly used antibiotics. It is also very effective in those persons hypersensitive to penicillin or other antibiotics.

The broad activity of "Ilotycin" is evidenced in its effect aganist penicillin-susceptible organisms and in laboratory tests against certain large viruses and Rickettsia like those causing typhus and Rocky Mountain spotted fever. Although not completely studied clinically at this time, laboratory tests indicate activity against undulant fever also.

Clinicians report that "Ilotycin" is not active against Gram-negative coliform bacteria, natural inhabitants of the intestinal tract which are destroyed by most other broad-spectrum antibiotics. Destruction of those organisms may be associated with diarrhea and may allow overgrowth of certain fungi, which in themselves may cause troublesome symptoms. Side-reactions associated with the use of "Ilotycin" are almost nil.

Structural analysis of the new antibiotic shows that its molecule contains no nitrobenzene group, sometimes thought to cause aplastic anemia. There has been no case of anemia reported in any of the clinicial trials. When the serum concentration is maintained at a high level, the drug crosses the barrier into cerebro-spinal fluid. "Ilotycin" is effective in oral administration.

SYNTHETIC VITAMIN A IN TREATMENT OF ECZEMA IN CHILDREN

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THE administration of therapeutic doses of Vitamin A to children who are allergic to fish or who cannot tolerate fish has long been a vexatious problem. Prior to 1947, the only source of high cencentrations of Vitamin A was fish liver oil which obviously could not be used in children allergic to fish. In 1947, Otto Isler described a synthesis of Vitamin A using citral from lemon grass as the basic raw material. In March, 1949, we received our first supplies of an aqueous dispersion of synthetic Vitamin A palmitate at a concentration of 25,000 units per cc.*

The purpose of our investigation was to determine whether synthetic Vitamin A could be tolerated in therapeutic doses by allergic children and if it would be effective in the treatment of eczema. Our experience during the past three years can best be described in the summaries of the following ten cases:

CASE HISTORIES

Case 1.—R. A., a ten-year-old boy with chronic eczema and asthma, had multiple sensitivities as revealed by clinical experience and the result of cutaneous allergy tests. The ingestion of fish upset the patient. Owing to the eczema and accompanying dry skin, synthetic Vitamin A was prescribed. He received 50,000 units twice a day for fifteen months, and 100,000 units twice a day for six months. The vitamin preparation was tolerated, and there was improvement in the skin condition.

Case 2.—S. B., a six-year-old girl with chronic eczema and very dry skin, was a member of an allergic family. Cutaneous tests revealed many positive reactors. There was no fish sensitivity by testing but fish frequently produced distress on ingestion. Synthetic Vitamin A was prescribed. She received 50,000 units twice a day for ten months. The vitamin preparation was tolerated, and its influence on the skin condition may have been beneficial since the child has shown improvement during the past year.

Case 3.—D. D. C. was a four and one-half-year-old boy with chronic eczema and asthma. The child had multiple sensitivities and cutaneous tests showed marked reactions to all fish allergens. Synthetic Vitamin A was prescribed. He received 25,000 units twice a day for a short period of time. An initial attempt to increase the amount made the patient ill. After a rest period of several months, the mother succeeded in giving the vitamin and the patient tolerated 50,000 units twice a day. He remained on this amount for six months. There was improvement in the skin condition but it was not entirely satisfactory.

Case 4.—D. C., a six-month-old boy, had eczema, very dry skin and a fish sensitivity. Synthetic Vitamin A was ordered and 25,000 units per day was taken for fifteen months. There were no signs of intolerance. The dryness of the skin decreased but the eczema was not influenced appreciably.

From the Department of Pediatrics, University of Minnesota Medical School.
*Made available for this study by Dr. M. J. Schiffrin, Hoffmann-LaRoche, Inc., Nutley, New Jersey.

Case 5.—M. D. was a nine-month-old boy with eczema and a very dry skin, who showed multiple sensitivities by clinical experience and cutaneous tests. The fish sensitivity was very marked. Synthetic Vitamin A was prescribed. The patient received 25,000 units per day for three months and then an increase to 50,000 units was made, and continued for one year. The preparation did not upset the child and the skin condition improved although there were periodical flareups.

Case 6.—J. K., a three-year-old girl with a very severe chronic eczema superimposed upon a dry skin, had a respiratory allergy also. Clinical experience and the cutaneous tests indicated a definite fish sensitivity. The child was placed on synthetic Vitamin A receiving 50,000 units twice a day. The preparation was given for eight months. There was no evidence of intolerance and the response was very good.

Case 7.—P. N. was a four-year-old girl with chronic eczema. She had numerous sensitivities from clinical observation and the cutaneous tests. The reaction to fish was negative but, clinically, the patient was distressed after eating fish. Synthetic Vitamin A was prescribed. She received 50,000 units twice a day for one year. The response has been very good.

Case 8.—T. S., an eight-year-old boy with chronic eczema with respiratory allergy had some sensitivities as shown by clinical experience and the cutaneous tests. The latter did not give marked reactions to fish; yet the child was unable to tolerate the ingestion of fish, in spite of the weak skin test. Synthetic Vitamin A was prescribed. He received 25,000 units twice a day for about three months, and then the preparation was increased to 50,000 units twice a day. The skin condition improved.

Case 9.—M. S. was a three-year-old girl with chronic eczema and dry skin. The cutaneous test revealed only a moderate sensitivity to fish but the child was unable to tolerate preparations containing fish oil. Synthetic Vitamin A, 25,000 units, was prescribed. In this case the child refused to take the preparation. The dosage was cut down to one-half and finally to one-fourth, but the child continued to refuse the Vitamin A preparation.

Case 10.—P. S., a five-year-old girl with chronic eczema, revealed clinical sensitivity to fish. This was not verified by the skin tests. Synthetic Vitamin A, in the amount of 50,000 units twice a day for ten months, was given. The response has been good.

DISCUSSION

Ten children from six months to ten years of age have been given 25,000 to 200,000 units of Synthetic Vitamin A per day for periods of from three to twenty-one months. One child *(Case 9)* was unable to tolerate the material. We have the impression that this was not due to the vitamin *per se* but was provoked by the flavoring agent added to the aqueous dispersion. Of the nine children who tolerated the vitamin, three showed some improvement and six had marked improvement of their eczema with a decrease in the dryness of the skin. There were no changes indicative of Vitamin A toxicity in this series.

CONCLUSIONS

1. Synthetic Vitamin A palmitate (Roche) can be given in therapeutic doses to children who are allergic to or who cannot tolerate fish.
2. Synthetic Vitamin A is of value in the treatment of the dryness and ichthyotic skin, which so often underlies infantile eczema.

THE ETIOLOGICAL DIAGNOSIS OF BRONCHIAL ASTHMA

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THE medical story of bronchial asthma takes one into many scientific fields, from the bedside to deep research. Its diagnosis and treatment demand a knowledge of its etiology. In a thorough study the physician becomes aware of the many organic chest lesions which manifest themselves as shortness of breath. Even proper symptomatic therapy becomes more intelligent when the therapist knows the causes of the patient's difficulty. A patient with asthma may wheeze one week because of being sensitized to ragweed pollen, the next week because of an acute respiratory infection, the next time because he has hurried upstairs, and again because he has lost his girl friend. In teaching undergraduate and graduate medical students, the following outline has been developed and has proven very helpful. This brief outline is presented as a framework to which more information and knowledge should be added.

BRONCHIAL ASTHMA

I. Pathology (changes are confined mainly to the functional structures of the lungs, in particular the small bronchioles).
   A. Decrease in size of the bronchial lumen
   B. Swelling of the mucosa with
      1. Hyalinization of the basement membrane
      2. Hypertrophy of the bronchial musculature
   C. Loss of cilia
   D. Change of the columnar epithelium to goblet cells
   E. Increase in the amount of mucus in the bronchial lumen
   F. Distention of the alveolar sacs
   G. Change in cellular and chemical content of the bronchial fluid
      1. Eosinophilia
      2. Neutrophilia and bacteria in infective cases

II. Physiology
   A. Abnormal breathing
      1. Prolonged expiration
      2. Shallow and rapid breathing
      3. Obstructive breathing phenomena
   B. Decrease in vital capacity
      1. Great increase in residual air
      2. Temporary emphysema
   C. Hypersecretion of mucus
   D. Interference in the exchange of gases
   E. Loss of ciliary action
   F. Pulmonary hypertension
      1. Increase in venous pressure
      2. Prolongation of right heart circulation time

From the Department of Allergy, Saint Francis Hospital, Pittsburgh, Pennsylvania. Presented in part before the Graduate Instructional Course in Allergy of The American College of Allergists, April 4-6, 1952, Pittsburgh, Pennsylvania.
Approved for publication July 16, 1952.

III. Etiological Diagnosis
- A. History
  1. Medical
  2. Allergic
  3. Infectious
  4. Psychologic and psychiatric
- B. Physical examination: includes detailed examination of the respiratory and cardiac systems, et cetera
- C. Laboratory work
  1. Routine
     a. Urinalysis
     b. Complete blood count
     c. Cardiogram
     d. Basal metabolic rate
     e. Roentgen examination of the chest and sinuses
        (1) Fluoroscopy; if shift of mediastinum, do bronchoscopy
        (2) Inspiratory and expiratory films
        (3) Bronchogram
  2. Allergy tests
     a. Nasal smear
     b. Differential blood count
     c. Skin tests
  3. Tests for infection
     a. Sedimentation rate
     b. White blood count and increase of neutrophils in the differential count
     c. Bacteriology of sputum
        (1) Cells
        (2) *Bacillus tuberculosis*
     d. Antibiotic susceptibility tests
     e. Skin testing with bacterial, fungus, and viral extracts
  4. Psychology and psychiatry tests
     a. Psychologic questionnaires
     b. Intelligence tests
     c. Projective psychologic tests
     d. Psychiatric interview
- D. Prognosis
  1. Vital capacity
  2. Venous pressure
  3. Circulation time

The pathology and physiology of bronchial asthma are not part of this paper, but a thorough knowledge of both yields gratifying dividends to the clinician as well as to the scientific worker.

HISTORY-TAKING

History-taking is the all-important study of the asthmatic patient. Thorough attention to details usually gives a brilliant reward. As knowledge of the related medical sciences increases, the more competent is the anamnestic investigator. Time and the willingness to give time are essential.

In the medical history one should review all the pertinent systems in the body in order to determine whether an organic lesion is a possible cause

of the shortness of breath. Discovery of a minute past medical experience might start the diagnostician on the etiological road. The cardiac and respiratory history should be especially explored. Is the patient short of breath on exertion? Does he have nocturnal dyspnea? Answers to these questions and many others should be obtained. An orderly medical history is essential.

As allergy plays such an important role in the etiology of bronchial asthma, this is the first specialized history to master when studying this type of patient. One must be skilled in the field of allergy to determine past allergic reactions and to obtain a thorough family history of allergy. One must know whether the shortness of breath precedes certain contacts with allergens or the eating of specific foods.

Many physicians do exceedingly well taking an allergic history on a plain sheet of paper. This is especially true if each patient's history is individualized and if the examiner has an orderly approach in questioning the patient. One individual might state that he has asthma only when he is exposed to ragweed pollen. The diagnosis of ragweed allergic bronchial asthma might be made by listening to one statement. The environment of the patient should be known. Often-times a visit to the home and working environment is all-revealing. Exact times should be noted, as the day of the week, time of day, seasons, et cetera. The proven exposure and reactions to common allergens indicate an allergic etiology. This makes further allergic study more intelligent, especially the skin testing. Complex chronic cases of bronchial asthma often necessitate elaborate questionnaires and allergy diaries. Many allergy specialists use routine forms which are given to the patient; these questionnaires explore the past allergic symptoms. If they are used, the patient must receive instructions as to how to complete the form. Time must be taken to review the completed questions. Patients are greatly disappointed if they take much time to complete the questionnaire or diary and the physician does not tell them that he has reviewed their answers. He must explain to them the significant findings.

An adequate allergy history should include a climatic history. Where has the patient lived? Where has he worked and played? Under what environmental conditions is he better or worse? The following meteorologic conditions should be considered:

1. Seasonal and daily temperature variations
2. Precipitation
3. Dampness
4. Humidity (the majority of patients are most comfortable in an atmosphere of approximately 50 per cent humidity. At 50 per cent humidity bacterial growth is supposed to be at a minimum)
5. Air currents
6. Daily percentage of sunshine
7. Barometric pressures

8. Abnormal substances in the environmental air
   a. Gaseous: fog, etc.
   b. Irritating chemicals: smog, etc.
   c. Organisms: bacteria, fungi, virus, etc.
9. Rapid changing of meteorologic conditions (the vasomotor instability of the allergic constitution cannot adjust to sudden changes.)

A detailed complete family history of allergy is especially significant.

The truly allergic asthmatic patient will give a negative history of infection. The history of a chronic infectious bronchial asthmatic patient, to be informative, may be long and tedious. Is the patient susceptible to bacterial invasion? To answer this one question, many questions may be necessary. He should be interrogated in a manner that brings forth environmental factors which favor infection. Is there any organ in his body which might be a focal point for chronic infection? The focus of infection might be found in any part or all of the respiratory system as well as in distant organs. Does his asthma become apparent when he is exposed to others suffering from true respiratory infection? When the patient states that he suffers from "frequent colds," questions should be directed to him to determine whether these are truly infectious, indicated by such symptoms as temperature increases, malaise, aches and pains, presence of mucopus in secretions, or reddened and inflamed membranes. The winter season in many geographical locations brings susceptibility to respiratory infections.

The psychologic and psychiatric history often becomes more intelligent if the physician makes his questions simple rather than too Freudian. Simple questions may instill confidence. The resulting preliminary simple answers often are followed by true facts, if it is necessary to delve deeper into the emotional and nervous imbalances or the social experiences of the patient. Often the emotional disturbance of the patient is very obvious, if the doctor takes a few minutes to talk to him casually and understandingly. Of course, it is assumed that the student of bronchial asthma admits that an emotional episode may produce an attack. It is only occasionally that the complexes are so deep seated that well-directed casual talk does not bring forth at least a suspicion of some psychiatric imbalance.

The general practitioner's approach to the patient is most fruitful in this type of history-taking. He must know his patient well. He must not antagonize him. It is necessary that he practice the art of medicine with skill and intelligence. He must know the patient's age, his wife, his children, his social environment, why he works at a certain job, and many other countless details. On the other hand, one must remember the pitfalls of blaming everything on the "nerves." Many patients do not accept this approach, or they come to the office rationalizing all as caused by their "nervousness." This type of history, to be successful, may take several interviews. One must be willing to admit that emotional imbalances are

important in the production of asthmatic attacks but must not be blinded to organic disease or allergic reactions. The evaluation of the psychologic and psychiatric history must depend on definite facts elicited from the patient; these facts must stand up under clinical observation. The student of bronchial asthma must realize, too, the difficulties of controlled psychological research. Later, more data will be presented which may enable the physician to approach this type of history-taking in a more intelligent manner. To conclude the discussion of history-taking, it should include study of personality development, one that brings out relationships to parents and to siblings, successes, frustrations, and the patient's general approach to life. It is important to get a clear picture of how the patient was living at the time of the onset of symptoms. Was there anxiety, frustration, emotional distress of any kind at the time of onset? Has there been conflict since the symptoms occurred? What is its nature? How does the patient react to the bronchial asthmatic symptoms? Is there shame? Guilt? Does patient avoid social contacts? Is the bronchial asthma exaggerated by any special life situations or what seem to be critical periods in the patient's life?

PHYSICAL EXAMINATION

One is often disappointed in obtaining little or no etiological information by physical examination. The extremely labored breathing of the asthmatic patient may often be heard many feet, yes, many rooms away from the patient. Often the most meticulous physical examination, with great attention to detailed stethoscopic examination, fails to provide any additional knowledge. Rarely thoracic observation reveals an organic lesion as an explanation of the shortness of breath. This is not a plea, however, for poor physical examinations. The individual's head should be examined thoroughly. A nasal speculum under penetrating bright light is necessary; without this instrument it is very difficult to evaluate the nasal cavity. One should remember that ofttimes the upper and lower respiratory tract will be alike, and one gets an idea of the bronchial mucosa by the picture seen in the nasal mucosa. If the nasal cavity presents an absolutely normal anatomy, one should be skeptical that he is dealing with true bronchial asthma. The differential picture of an allergic nasal mucosa and an inflammatory one should always be remembered. Many times meteorological factors influence the appearance of the nasal mucosa, making this differentiation difficult. Most experts are ready to admit that often one cannot differentiate allergy from infection by nasal examination alone. A good view of the mouth under proper light is important, including inspection of the teeth, gums, and tongue. A skilled examiner will expose the tonsillar fossae, especially when dealing with children. Many physicians hurriedly place a blade on a struggling child's tongue and when finished have no idea whether or not the patient has any tonsils. In all examinations the diagnostician must remember that there is inspection,

palpation, percussion, and auscultation. He must study the cardiac system well, and take the blood pressure. The allergic patient often has a low pressure. In rare instances a complete body examination is indicated, in which distant foci of infection might be uncovered. A tumor which has metastasized to the lungs may be discovered.

LABORATORY WORK

The diagnostician must know the laboratory tests which might aid in the etiological diagnosis of bronchial asthma and use the proper ones when necessary: urinalysis, blood count, cardiogram, and basal metabolic rate.

An expert roentgenologist doing a complete roentgen examination of the chest and sinuses gives the thoracic examiner much help. He should be consulted frequently for every patient. If only one type of roentgen examination is available, fluoroscopy gives the most information since with fluoroscopy one may observe the abnormal lung functions under living, breathing conditions. If, on repeated fluoroscopic observations and after bronchodilating therapy, the patient still shows an irreversible shift of the mediastinum, our rule insists upon bronchoscopy.

The x-ray study of the asthmatic chest should include the following logical steps:

1. Fluoroscopy of the chest and sinuses. This examination is used as a preliminary study from which other x-ray studies are decided upon.
2. Posterior-anterior x-rays at full inspiration and at full expiration. These views are highly desirable, especially if fluoroscopy is not available.
3. Other views, as oblique, laterals, stereoscopic, et cetera, to bring out more exact delineation of any abnormal area not shown with posterior-anterior exposure.
4. Bronchography with opaque oil. (It must be remembered that allergic patients may not tolerate iodinized oil.) Bronchial and lung mapping with or without bronchoscopy.
5. Body section roentgenography employing planographic plates through serial section x-ray of a localized involved area.

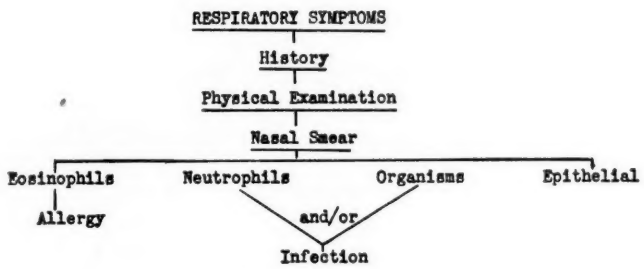
The fluoroscopic observation for mediastinal shift has made it possible for us to make an early diagnosis of resectable bronchial cancers and to find a few foreign bodies, as well as to discover tracheobronchial tuberculous lesions.

ALLERGY TESTS

Three laboratory tests are extremely important in the allergic management of bronchial asthma. They are nasal smears, differential blood counts, and skin tests (scratch and/or intradermal). The presence of many eosinophils in the nasal smear is definite evidence of an allergic response. Frequent smears are often necessary to discover the eosinophils. Our experience with the study of over ten thousand preparations leads us to

believe that the nasal smear is by far the most important laboratory test to be used by the allergist dealing with respiratory disease. Every student should know the Hansel technique, which is simple. One need not stimulate the nasal mucosa for secretion. If there is a large amount of

CHART I



The major responses in the nasal smear are:

a. **Allergic:**
E++++ N 0 Or 0 Ep +or 0

b. **Infectious:**
E 0 N++++ Or++++ Ep +or 0

c. **Bacterial allergy or a secondary infection superimposed on an allergic response:**
E++ N++ Or+++ Ep +or 0

exudate present at the examination, a sample may be taken. Otherwise, the patient takes home two clean slides, toothpicks, and Kleenex and brings the prepared slides along at the next visit. This allows taking the secretion easily when it is adequate. Any polychrome stain, such as Wright's, may be used for staining. The slide may be searched with all powers of the microscope, but the oil immersion is most revealing and its use is imperative.

The accompanying diagram (Chart I) should always be fresh in the diagnostician's mind.

Nasal smears are best secured through the anterior orifice of the nasal passage. Sputum is not as reliable as nasal secretion. A concise, excellent monograph titled "Cytologic Diagnosis of Nasal, Bronchial and Ocular Secretions with Hansel Stain" is available from the Lide Laboratories, Inc., Saint Louis, Missouri.

The differential blood count is packed full of information. Allergy is the most frequent cause of an eosinophilia, that is, a rise of 5 per cent or above; 3 per cent to 5 per cent is borderline. Two hundred cells should be counted, fifty cells on each border of the blood smear (Fig. 1).

One should be experienced in blood smear technique in order always

to make the smear the same. In this way a crude estimate of the number of red and white cells might be determined. A sound knowledge of hematologic cells is a great help. Variations and maturity of white and red cells must be observed, as well as the presence of blood platelets. A count

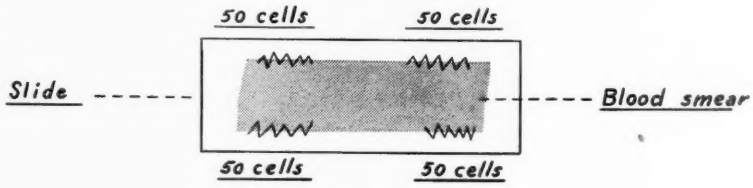


Fig. 1.

of 3 per cent eosinophils is considered normal but does not rule out allergy. If an allergic reaction is acute, there is more possibility of finding an increase. Other diseases may be responsible for an eosinophilia. Congenital eosinophilia has been reported many times. Here many blood relations may show an unexplained eosinophilia on repeated blood differential counts. The workers with ACTH and cortisone have made the circulating eosinophil count very popular, and this method may be more accurate for the exact determination of eosinophils but should not displace the simpler technique of differential counting.

Skin tests have been studied and written about so much that there is little to add. In spite of the recent adverse criticism, they still are an integral part of the allergy laboratory studies. Scratch tests are safer. Using equal strength extracts, a rule of thumb is that the intradermal test is a hundred times more sensitive than the scratch. It is extremely important to realize that a severe constitutional reaction may occur in a highly sensitive patient no matter what type of testing is employed. Deaths have been reported even by the scratch method. The diagnostician must know his extracts, know the patient, and know how to interpret testing! In the evaluation of skin tests it should be remembered that no laboratory test gives the clinical diagnosis. Better testing, I am sure, will be forthcoming. One should have a plan to study in detail patients in whom false positive and false negative tests are encountered. The many clinical ways of testing allergens should be more widely employed. The skin testing should be thorough, thoughtful, and individualized to meet the patient's problem. I myself prefer intradermal testing because a highly sensitive technique is often desired to bring out positive allergens. The physician should manage and guide the skin testing and not put it entirely into the hands of his laboratory technician. In the office, our own method is to inform the technician daily just what tests are desired on each patient. She places the tests upon the patient and sets the reading

time on an alarm clock. When the alarm rings, the physician goes to the test booth, reads the tests, and talks to and treats the patient.

TESTS FOR INFECTION

Many cases of bronchial asthma have both an allergic and an infectious etiology. Some prove to be due to infection alone. Bacteriologic laboratory proof of infection, suspected by examination of the respiratory system, is sound medical practice and should not be confined to so-called research. Nasal smears for cells of infection and bacteria, and culture of sinus washings, tonsillar tissue, teeth, or bronchoscopic secretions take one away from "barnyard" medicine. Cultures are often needed for the proper use of bacterial and virus vaccines. The bacteriologist must be informed when an autogenous vaccine is desired. The proper bacteriologic study of the sputum, in some instances, establishes the presence of bacterial infection. In rare instances, it may help to prove the presence of a fungus infection or a tracheobronchial tuberculous infection.

Sometimes a depressed sedimentation rate makes one search more diligently for evidence of infection. Certainly an increase in the white blood count and/or "a shift to the left" of the neutrophils in the differential is highly suggestive of infection. In status asthmaticus I use these findings in hospital cases as an indication for the use of antibiotics.

In ordering antibiotic susceptibility tests the diagnostician must be sure to obtain deep sputum and immediately before any secondary bacterial or contaminating growth occurs must complete the "seeding" of the secretion on the culture plates. Using the rapid technique the antibiotic discs are already on the culture medium of the plate. Nurses should be constantly informed that speed is an essential factor in the success of this procedure. Proper collection and rapid handling of the sputum cannot be overemphasized. Personal experience has helped me to control infections in asthmatic patients by changing the antibiotic, based on the results of this test.

In spite of the controversial nature of skin testing with bacteria, fungi, and virus extracts, they are still a part of my approach to the problem of infection. Our lack of knowledge concerning the complex nature of bacterial sensitivity is a definite barrier to the interpretation of our findings. These tests are always read in fifteen minutes and also approximately forty-eight hours later to record the immediate as well as the delayed reactions. The application of these tests does give help, and the constant use by many investigators might bring fruitful knowledge to this intricate field. My own experience with bacterial testing has given me an intelligent approach to the use of bacterial vaccines as well as the more recent virus vaccines. It has been definitely noted that specific allergic reactions may be experienced on testing a specifically sensitive patient with bacteria, fungi, or virus. Treatment extracts or vaccines of these organisms may also produce constitutional reactions.

PSYCHOLOGICAL TESTS

The psychologists and psychiatrists have literally flooded their journals and books with questionnaires to show how one might obtain psychoanalytic material from the patient. Many of these contain references for those

CHART II

PSYCHOLOGICAL TESTS

Number of times each used

Intelligence		Personality	
Wechsler-Bellevue	14	Rorschach	14
Stanford-Binet	1	Thematic Apperception Tests	6
Goodenough	1	Human Figure Drawing	3
		Bender Visual Motor Gestalt	2

All of our psychological tests are given and interpreted by Miss Zita Okinak of Pittsburgh, a trained medical psychologist. In difficult situations she has consultation with Dr. Edward J. Carroll, Associate Professor of Psychiatry, University of Pittsburgh School of Medicine, who has a good insight into the relationship between allergy and emotional imbalances.

interested. After studying a few papers and books, the diligent physician is equipped in a small way to approach the emotional and psychogenic problems of his bronchial asthmatic patients. Then, if he wishes to use the questionnaires, they are best written by himself in consultation with a good medical psychologist and/or psychiatrist. Many simple questions may be included to establish how the patient accepts his age, social position, work, relations, financial position, et cetera. To get the best results these questions should be mingled with others directed to the medical symptoms of the patient. There are a large number of related symptoms which point to a psychoneurosis. If the patient gives a positive response to a number of these symptoms, a neurogenic imbalance should be suspected. The questions should be subtle but not confusing. The patient's respect for and confidence in the physician are a great help. These questionnaires should not be given to the patient at the first few visits. The physician must wait for the opportune time, because if he antagonizes the patient, all is lost! He must make it a practice before presenting a patient with a questionnaire of this type to explain clearly the role of the psychosomatic imbalances in the production of asthmatic attacks. These studies may be made while other procedures such as allergy skin tests are being done.

In our recent report of intelligence tests and projective psychological tests applied to bronchial asthma, we were surprised to find that the intelligence tests are informative. Intelligence tests, however, are not vital, since it is reasonably simple to obtain much of this information by a short interview with the patient. How far the patient progressed in school, et

cetera, are the questions to be asked. I prefer the Wechsler-Bellevue test because of the interview style of technique and because it will often give incidental information regarding personality characteristics.

There are a fairly large number of bronchial asthmatic patients with deep emotional conflicts. These imbalances, primarily or secondarily, play an etiological role in the production of some of the attacks. These individuals often need psychiatric therapy but will not accept formal treatment nor seek a psychiatrist. They must be understood and treated by the physician who is directing the etiologic studies. The diagnostic physician in these cases must not only know the basic principles of psychiatry but must have at hand all the psychological laboratory help which he may need. Sometimes several directive or nondirective psychiatric interviews will easily resolve the emotional conflict. If the physician is unsuccessful by interview, he can obtain help by employing projective psychologic testing. In these tests the patient often unconsciously reveals a deep conflict. In our own practice the patient is told that he is being sent to the psychologist for testing. She attempts to make the patient comfortable by first taking a personality history. She then explains the testing to the patient. Several intelligence and psychological tests are completed. The technician then studies the results, making the psychological interpretations before much of the medical data is given to her. The results are then presented to the physician, who gives the medical history and laboratory findings of the patient. His impressions of the individual's personality are compared with the test data.

Patients with definite psychosomatic or psychogenic problems should have an opportunity to consult a psychiatrist or a physician trained in the diagnosis of bronchial asthma who knows the importance of all the etiological factors including the psychologic. A psychiatrist who attends this type of case must be willing to admit the many pitfalls of psychoanalytic therapy. Most of the therapeutic measures employed in this field often fail. It is important to realize that psychosomatic or psychogenic asthma patients may die in an attack, and a knowledge of the ordinary symptomatic therapy for asthma is needed for them just as for all other types of severe cases. Most of the front-line psychiatrists, who really appreciate the medical problem of bronchial asthma, confine themselves to the psychiatric therapy of the patient and ask that the general etiologic studies and therapy be managed by a physician trained in this field.

PROGNOSIS

There are three laboratory tests that certainly belong to any well managed etiological study. They are (1) vital capacity tests, (2) venous pressure and (3) circulation times of both right and total circulation. These are absolutely essential for an intelligent prognosis. There are many patients labeled "chronic asthma" in whom the physician does not know that an irreversible pathologic process such as emphysema is present. A wise

examiner will cautiously inform the patient that a complication is present which will probably cause some difficulty the remainder of his life. This often stops this type of patient from shopping from physician to physician, ending finally in the grasp of some charlatan.

The complications of bronchial asthma are

1. Bronchial occlusion due to spasm, edema, or stenosis. This may be partial or complete
2. Emphysema, reversible or irreversible
3. Atelectasis
4. Bronchiectasis
5. Bronchial or respiratory inflammations
6. Mediastinal emphysema, with or without subcutaneous involvement
7. Spontaneous pneumothorax
8. Cardiac dysfunction, pulmonary hypertension with acute or chronic right heart failure. In rare instances the right cardiac mechanism might withstand the increased pressure and the patient finally develops peripheral cardiac failure
9. Periarteritis nodosum
10. Traumatic injury to the thoracic tissues including fracture of ribs. This is the result of extreme pressures in the chest from severe sneezing, coughing and/or wheezing.

Vital capacity readings, venous pressure, and circulation times are simple tests and may be accomplished easily in the physician's office.

There are many elaborate types of vital capacity apparatus. The most scientific will give a reading of each lung separately, and this technique should precede any complex lung surgery. In order to interpret this function of breathing, one should know the normal and abnormal physiology of respiration and what ordinary factors influence vital capacity. It should be remembered that vital capacity may be easily studied by clinical observation on the patient. An acute asthmatic attack always depresses the vital capacity. For prognosis frequent readings are necessary, and the highest reading secured while the patient's symptoms are quiescent is the important one. For its ease and quickness of operation, plus its cheap availability, a bellows vital capacity machine is used extensively in both office and hospital practice. With a large number of sterile breathing tubes at hand, the number of readings that can be taken in a short period is almost unlimited. Young student physicians especially should be trained in the frequent application of this test, so that in practice they might be able to judge clinically the vital capacity of respiratory patients. One must realize that for research the bellows machine has a certain percentage of error. This error may be kept to a minimum by instructing the patient accurately in the technique of carrying out the test and also keeping the apparatus in good working condition. An occasional comparison with a water manometer machine will help.

Venous pressure readings are often the first signs of right heart stress. It has been seen that the venous pressure of a patient undergoing a sustained asthmatic attack tends to increase. As the attack becomes controlled

the high level of venous pressure may or may not decrease. If it does not rapidly or slowly decrease, there is evidence of chronic right heart hypertension. When one is giving frequent intravenous therapy to a patient in status asthmaticus, a simple routine is to take a venous pressure reading with every insertion of the needle. This procedure aids greatly in the adjustment of fluid intake and other important symptomatic therapy.

There are many techniques and drugs employed for circulation times, none of which is completely objective. The technical physician will attempt to carry out the details of this test in a fashion that allows for interpretations. Trained personnel is a great asset. Our technique calls for the rapid placing of about four drops of ether in a solution of Decholin after the personnel and the patient have been alerted and instructed. Thus by one technical maneuver both right heart circulation time and total circulation may be recorded. In this technique the patient's experiences are rapid, and everyone must be alerted to the quickness of the breathing forth of ether as well as the bitterness in taste. The technique and drugs used must always be recorded. This is especially important if one changes his drugs from time to time. On later review of the records the figures will then lend themselves to proper statistics.

SUMMARY

In our office practice only one new patient is taken daily, and the appointment is for at least one and a half hours. During this time the consulting physician takes a complete history on plain sheets of paper, following the various medical topics as outlined. The physical examination then follows, with special observations directed to the head and chest. Other examinations are made as suggested by the patient's conversation. The preliminary diagnosis, instructions, and symptomatic therapy are then outlined. Written instructions by the physician are excellent reminders to the patient. If the individual is to receive a history questionnaire, allergic diaries, routine hay fever directions, et cetera, they should now be explained. Vital capacity is determined. The technician takes two differential smears and shows the patient how to obtain nasal smears. Most patients are sent to the roentgenologist for fluoroscopy of the chest and sinuses and x-rays as indicated. All patients with depressed vital capacity get an x-ray or must have had an acceptable recent one. At the end of this first visit the patient is told whether skin tests are necessary. The purpose of the skin tests is outlined. The patient is given a second appointment to begin the skin tests or for re-examination.

Our patients are sent to the hospital for severe uncontrollable asthma or for thorough study. Some are old patients and others have been directly referred there. At the Saint Francis Hospital a small but complete allergy department and laboratory helps immensely. An uncontrolled, severe, hospitalized bronchial asthma patient is usually submitted to the following laboratory tests:

1. Urinalysis
2. Complete blood count with a differential study
3. Bacteriology and antibiotic sensitivity tests of fresh deep sputum, including several sputa for *Bacillus tuberculosis*
4. Nasal smear, sent directly to the allergy laboratory
5. Fluoroscopy of chest and sinuses and x-rays as indicated
6. Blood serology
7. Sedimentation rate
8. Vital capacity
9. Circulation time, total and right heart; most patients receive an electrocardiogram
10. Venous pressure
11. Projective psychological tests.

Vital capacity, circulation times, and venous pressures usually are done when the patient has recovered from the attack.

The etiological study of asthma is serious medicine. An acute, severe attack of bronchial asthma is a medical emergency, as a patient may die in his first attack as well as in any subsequent one.

Deaths in asthma are due to:

1. Complete physical depletion associated with "the alarm reaction"
2. Severe breathlessness ending with respiratory failure
3. Emphysema with collapse of vital capacity
4. Anoxemia
5. Right heart failure
6. Periarteritis nodosum
7. Other medical complications

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SECTION ON ALLERGY
MEDICAL SOCIETY OF THE COUNTY OF KINGS

The Section on Allergy of the Medical Society of the County of Kings and Academy of Medicine of Brooklyn held a meeting on Thursday, November 20, 1952, at Brooklyn.

The paper of the evening was "Penicillin Sensitivity—Clinical Manifestations, Diagnosis and Desensitization" by Samuel M. Peck, M.D., dermatologist associated with Columbia University, New York Medical College, and Mt. Sinai Hospital, New York.

ALLERGY RESIDENCIES AVAILABLE

There are several approved allergy residencies available on July 1, 1953, at the Medical Center, School of Medicine, University of Pittsburgh, and the United States Veterans Hospital in Pittsburgh, Pennsylvania. The residencies are part of the program of training in Internal Medicine. They include a large out-patient allergy department, a good in-patient service and ample opportunity for allergy laboratory experience and some clinical investigation. Stipend ranges from $1,500 to $3,500 per annum.

All interested, please contact Leo H. Criep, M.D., May Building, 119 Fifth Avenue, Pittsburgh, Pennsylvania.

MESQUITE AND RELATED PLANTS IN ALLERGY

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and
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THE purpose of this paper is to present our experience with mesquite and closely related trees and shrubs in the production of allergic symptoms with the hope that the discussion will add to the general knowledge of this family of plants and their place in the diagnosis and treatment of allergic disease.

Mesquite *(Prosopis juliflora)* is one of the most common trees of Southwestern United States. While much has been written about the mesquite in regard to its economic importance, spreading, distribution and eradication, there is still lack of agreement as to its correct naming. Mesquite has brought about a striking change in the appearance of the Texas range, and has been listed as the number one enemy of the ranchman and foremost among the noxious plants of Texas. While it is being attacked by nature's and man's most potent weapons, it appears to be steadily holding its own.

When the white man first came to the Texas frontier, he found a stock farmer's paradise. He found here vast areas of native prairie grasses suitable for grazing, and scattered open areas of fertile soil suitable for cultivation. Here and there in these vast prairies, the early settler found many small areas covered by numerous species of present-day noxious brush forms. In the Rio Grande Plain were found mesquite *(P. juliflora)*, huisache *(Acacia farnesiana)*, and huajilla (pronounced wa-he-ya), or cat's-claw *(Acacia greggii* and *roemeriana)*, also known as chaparral.

These noxious forms were of little interest to the pioneer. The dominant vegetation was composed of the tall and short grasses native to the area, and any intruder would be crowded out quickly. The early settlers did not take the time to study the balance nature had established in this empire of grasses. Man, aided by the elements of nature, destroyed this balance, permitting and aiding the spread of these particular trees and shrubs until they now seriously affect an estimated 71 million acres of rangeland in Texas and Oklahoma. With the wide spread of these trees and shrubs, we are now confronted with the allergies caused by them.

BOTANICAL CLASSIFICATION

Botanically, mesquite has been placed in the leguminosae or pea family and given the generic name of *Prosopis*. This genus contains over forty species of trees and shrubs in various parts of the world. The most

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common mesquite *(P. juliflora)* has three varieties: *Glandulosa, Torreyana* and *Velutina.*

The leaves of mesquite are pinnately compound with rather fine leaflets. The flowers are white and borne in cylindrical catkin-like heads that turn yellow with age as the anthers mature. The flowers are insect pollinated mainly by bees that visit the flowers for the nectar and pollen. The pollen when dry is also picked up by the wind and may be carried a considerable distance.

The pollen appears to consist of two forms, spherical and elliptical, resembling a football. This football-shaped pollen has a fold in its wall, and if water is added the pollen grain becomes spherical as the water is absorbed.

In the areas of low rainfall, mesquite is reduced to shrub form. In the northern limits of its distribution it also frequently freezes back as well as being reduced to shrub form. According to Bogusch,[1] its distribution is limited by climatic factors—rainfall and temperature.

GEOGRAPHICAL DISTRIBUTION

The genus *(Prosopis)* or mesquite with its forty species of shrubs and trees has a rather wide distribution and may be observed growing from Louisiana west through Texas, New Mexico, Arizona, and into California. To the north it can be found near the Kansas line in Oklahoma, and to the south all through Mexico and as far south as Chile. Some species are also found in portions of tropical Africa and in southwestern tropical Asia. This genus is also well represented in Argentina and Uruguay, where it supplies commercial timber.

Our survey indicates some variance in distribution from that pictured by Vaughan[4] in his *Practice of Allergy,* First Edition, 1939. We find a heavier concentration in Oklahoma and East Texas and none in Kansas.

The common mesquite *(P. juliflora)* is the one which occurs in the Southwestern United States, most of Mexico, Central America and the West Indies. It has been suggested that mesquite is one of the alien members of our flora, having come in from the eastern flank of the Andes in Argentina.

Mesquite is believed to have been introduced into Hawaii by the Jesuits, where it has become an important source of timber as well as providing nectar for bees.

POLLINATION

Seasons of Pollination.—Mesquite has been observed in flower from March through November. The height of the flowering season, however, occurs during April, May and June. During the dry seasons, it has been observed to flower following each rainfall. While the mesquite is visited by bees and other insects, on hot, dry days the pollen is picked up by the wind and carried for several miles.

Pollen Count.—The daily pollen count of mesquite has been observed to be relatively low when compared with oak, mountain cedar, or ragweed. The daily average observed during the flowering season was twelve to fifteen pollen grains per cubic yard with a maximum count of 157, although higher counts may be obtained if a pollen slide is placed near a mesquite thicket in flower. A person driving along a highway past a mesquite thicket may pass through these high pollen counts during the flowering season.

Collecting Pollen.—Mesquite pollen in large quantities is rather difficult to collect. Since the flowers on a cluster do not all shed their pollen at the same time, only a small percentage of the pollen is obtained when the entire clusters are gathered. The best results are obtained by picking the catkin-like flowers early in the morning and then collecting the pollen as the anthers are opened. However, this is still a relatively slow method.

Extraction of Pollen.—Dried mesquite pollen extract, 3 Gm per 100 cc, is difficult to filter because of gel formation. With some collections of pollen we have had to cut our stock concentration to 1 Gm per 100 cc because 3 per cent would not filter. Experience indicates that extract prepared from non-defatted mesquite pollen gives better results.

OTHER CLOSELY RELATED PLANTS

Retama *(Parkinsonia aculeata),* another member of the leguminosae, is a small tree or shrub with thorny green branches and drooping foliate. The leaves are pinnately compound. The long, flattened central axes are edged with tiny leaflets. Yellow flowers turning orange with age, are produced in elongated, drooping clusters. The trees were observed flowering from April through September with an increased flowering following heavy showers. Except for its greater translucence, the pollen of retama closely resembles that of Spanish oak and may be confusing to the pollen counter in the summer months. The pollen of retama is rather heavy and somewhat sticky. It has been observed on the slide occasionally but is probably not carried any great distance by the wind.

Huisache, or sweet acacia *(Acacia farnesiana),* forms a small tree or shrub, usually with several stems arising from the same root. The leaflets are very fine and sensitive. The flowers form a yellow fuzzy ball about the size of a small marble, and consist largely of clusters of yellow stamens. The flower balls turn orange with age. Flowering dates are from January to the first week in April and frequently the flower buds are killed by late freezes. The pollen is rather large and heavy but does occasionally appear on the slide. Since it flowers rather early, the pollen is important to the bee keepers. However, because of its erratic flowering, it cannot be depended upon. This also makes it rather unimportant as a plant causing hay fever.

That group of shrubs usually referred to as devil's-claw, cat's-claw

chaparral, or huajilla (wa-he-ya), also belong to the acacias *(A. roemeriana), (A. greggii), and (A. berlandieri)*. These plants usually grow in clusters of two or three shrubs and are frequently associated with persimmon and agarita. They are an important source of honey; however, they are also undesirable since the thorny clawed branches are rather rough on clothing and skin.

The flowers consist of many tiny individual blossoms in globular heads, the size of small marbles. The fruit is a flat pod five inches long and one inch broad that turns red as it ripens. The flowering time is February, March and April but frequently the plants flower again in September and October. The pollen being rather large and heavy, is probably not carried any distance by the wind. However, any person walking in the vicinity of these shrubs at flowering time may inhale a considerable number of pollen grains.

SKIN REACTIONS

Because of the heavy distribution of mesquite in our area, testing with this antigen is routine. Checking the records of 700 cases of allergic disease, we find the incidence of mesquite reactions to be as high as 55 per cent.

Some years ago we checked 100 allergic patients with huisache and retama extracts and found no positive reactions. Swinny concludes that these are not antigenic.

CLINICAL SENSITIVITY

Although we see many cases of dermatitis venenata, Swinny has never observed one due to the mesquite family; Bieberdorf has seen one, a Mexican laborer. Of the 385 patients with postive reactions to mesquite only thirty-seven could be correlated with active pollination. Thus the incidence of false positive reaction is very high. No cases of atopic dermatitis were found due to mesquite, a condition fairly frequently seen due to cedar and grasses, less frequently with the amaranths and ragweeds.

Of the thirty-seven clinical sensitivities, twelve presented conjunctivitis (some quite severe) as the chief complaint. The ratio of conjunctivitis among mesquite-sensitive patients is remarkably higher than to other pollens. Brunner and Bieberdorf[2] observed that eye injuries resulting from mesquite thorn were much more severe than a similar type of injury caused by a wood splinter. It is possible that the irritant found on mesquite thorns is the same as that found in mesquite pollen.

CONCLUSION

The mesquite and *acacias* as a whole are usually considered to be relatively unimportant as hay fever causing plants except in the Southwestern United States. Definite conclusions as to their importance in causing hay fever have not been established, except for the mesquite which war-

rants consideration in the mesquite-growing areas. There are over 400 species in this group, composed mainly of small trees or shrubs and occurring mainly in the arid regions of the world.

The flowers, in general, have the appearance of not being wind pollinated, and most of them produce a rather, heavy, sticky pollen. The flowers are regularly visited by insects. In some species, the pollen grains cling together, forming tetrads. Although the pollen is not produced in great abundance and is not readily carried by the wind, isolated grains do appear on pollen slides.

While the status of the *acacia* pollen in the causing of hay fever is not quite clear, Rowe[3] found it to be very toxic, even in small quantities, in causing not only hay fever but also dermatitis. Swinny, Rouse and Bieberdorf have failed to verify these findings.

Since many of these trees and shrubs are planted as ornamentals, it is within the realm of possibility that the pollen grains are inhaled while in the immediate vicinity of the plants.

In regard to mesquite, there is no doubt that it does cause hay fever in certain areas of the Southwest; however, while it is classed as being of secondary importance, it does warrant consideration.

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CHEMICALS IN FOODS AND COSMETICS

All allergists should be interested in the three comprehensive reports on chemicals in foods and cosmetics which were brought out in hearings before the House Select Committee. These hearings were held before the House of Representatives, the Eighty-first and Eighty-second Congresses.

It was also brought out at these hearings that adipose tissue, with its many important functions, can be influenced by the presence of cumulative poisons such as the chlorinated hydrocarbon insecticides. Among the more important of these are DDT and TDE. The accumulation of these insecticides in fat tissue shows that the tissue acts as a biologic magnifier for the insecticide. By experimental studies on rats, it has been shown that its accumulation in the fat can be up to thirty times the level of intake.

Hundreds of expert witnesses were called to testify and many important facts were brought out regarding allergies due to cosmetics of all types.

The reports, "Chemicals in Foods and Cosmetics, Hearings Before the House Select Committee to Investigate the Use of Chemicals in Foods and Cosmetics," are in three parts. Part 4 is a cumulative list of witnesses and index.

Copies may be obtained by writing to Dr. Irvin Kerlan, Federal Security Agency, Food and Drug Administration, Washington 25, D. C.

FURTHER NOTES ON THE CLINICAL USE OF AMBODRYL HYDROCHLORIDE

A Summary of the Clinical Observations on 81 Patients Receiving the Capsular Form and Some 60 Patients Receiving Elixir Ambodryl Hydrochloride

J. WARRICK THOMAS, M.D., F.A.C.A., and FRANK R. KELLY, JR., M.D.
Richmond, Virginia

SINCE the initial report we made in February, 1951, on the "Clinical Evaluation of Ambodryl Hydrochloride, A Report of 100 Cases,"[1] we have had the opportunity of carrying out a further study.

AMBODRYL HYDROCHLORIDE (CAPSULAR FORM)

We have treated an additional eighty-one cases with capsular form of Ambodryl (25 mg). The length of treatment of some of these patients has varied from one day up to a period of twenty-six months. In fact, one patient, age eight, with an atopic dermatitis, has received Ambodryl on a daily dosage of from one to six capsules per day for twenty months. An adult patient with an allergic rhinitis received the drug over a period of two years with excellent control of his symptoms, the dosage varying from two to four capsules per day. There have been some six patients who have been very demanding in their requests for further supplies of the drug after having tried other antihistamine drugs with side reactions and report that this was the only preparation that they were able to use with control of symptoms unaccompanied by side reactions.

No attempt was made in this communication to go into the details of the different clinical conditions in which the drug has been used as the proportion of the patients and results of therapy has been comparable with the initial report.* The reactions have been minimal and in no instance has there been any severe side reactions. On one occasion, there was drowsiness of sufficient severity to warrant discontinuing of the drug

The capsular form of Ambodryl was placed on the market on July 11, 1952, in Richmond, Virginia, and in certain other localities.

ELIXIR OF AMBODRYL HYDROCHLORIDE

A clinical study of Elixir of Ambodryl was carried out with some sixty patients—more of the pediatric age—and an excellent response to this drug was appreciated. We were not advised by the Parke-Davis Company as to the characteristics or constituents of Elixir of Ambodryl which is a light amber, clear syrup containing 10 mg per 4 cc.

There were only about six of the sixty patients who felt that they did not appreciate sufficient relief to warrant continuation of the drug.

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*Thomas, J. Warrick, and Kelly, F. R., Jr., "The Clinical Evaluation of Ambodryl Hydrochloride, A Report of 100 Cases," ANNALS OF ALLERGY, Vol. 9, 481-486, July-August, 1951.

The palatability of the drug was satisfactory in that most of these patients did not object to the taste and the administration of the drug proved to be no problem to the mothers.

The dosage of Elixir of Ambodryl has varied from drams 1 (10 mg) to drams 2 (20 mg) four times a day, or as was necessary, for a duration of from approximately one day to eighteen months. The need of an elixir form was appreciated prior to the preparation of same by the Parke-Davis Company, and was indicated in our initial report, two patients were placed on a prescription containing Ambodryl, 300 mg, glycerine, 10 cc, Simple syrup, quantity sufficient to make 120 cc, which was comparable to the dosage (10 mg) per dram in the elixir subsequently supplied for clinicial trial. These patients received the above prescription over a period of time from one day up to two months including one or more of the pollinating seasons.

The primary group of patients in which Elixir of Ambodryl was used consisted of those having a respiratory allergy and pruritic allergic dermatoses.

There were also instances in which the Elixir of Ambodryl was used in patients who had not only a respiratory allergy but a superimposed infection and no unusual or remarkable observations were made in this group.

SUMMARY AND CONCLUSIONS

Elixir of Ambodryl was found to be palatable and well tolerated without significant side reactions. The control of symptoms in those patients for which the drug was used was approximately the same percentage as the capsular form, or above 75 per cent. The availability of an Elixir form of Ambodryl appears to be warranted.

2031 Monument Avenue

"SMOG" AND ASTHMA

More specific evidence that air pollution is of increasing importance in the aggravation of respiratory allergies has been furnished recently by the unusual "smog" occurrence in London and environs on two occasions during the month of December. It was estimated that there was five times the number of tons of dust particles which normally fall in London.

Even cattle at a livestock show choked and died from the concentration of the "smog." Many asthmatics were seriously affected, their conditions aggravated, and some patients developed asthma for the first time. Deaths from asthma were somewhat comparable to the Donora Catastrophe.

The first blinding mist the first week in December was held responsible for 2850 deaths. Air and sea traffic in London and other major English cities were halted by the fog, and motor vehicles were moving at a crawl. Visibility in the port of London was down to 60 yards as a result of this concentrated "smog."

ALLERGY IN SINUSITIS

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THE paranasal sinuses stand at the entrance to the respiratory tract. Embryologically[1] these cells represent excavations of bone which become lined with simultaneously advancing epithelium from the nasal cavity. The nasal epithelium, originally a part of the mouth cavity and now respiratory in function, covers the turbinates and lines the vomeronasal organ, the ethmoid cells, and other paranasal sinuses. Histologically[6] the same pseudostratified ciliated epithelium is to be found covering both the upper and the lower respiratory tract. In view of these facts it is not surprising to find that certain pathologic changes in the upper and lower respiratory tract are intimately related to each other.

Our knowledge of the role played by allergy in diseases of the paranasal sinuses is of quite recent origin. Only twenty years ago Professor Hirsch[13] summarized the prevailing viewpoint when he classified sinus disease as of two types, suppurative and catarrhal. In suppurative sinusitis there was moderate swelling of the mucosa lining the sinus, together with purulent or mucopurulent secretion. In catarrhal sinusitis, according to Hirsch, the mucous membrane became very edematous, so that there might be no air space in the sinus at all, and perhaps only a little serous secretion, which would make the return flow from irrigation of such a sinus quite clear. When the edema extended to the region of the ostium of a sinus, polypi appeared in the nose. Hirsch taught that recurring polypi were due to prolapsed mucous membrane in catarrhal disease of the accessory sinuses, and he found that 60 per cent of the cases of polypi originated from the maxillary sinus.

It is not difficult nowadays to recognize the allergic etiology of the catarrhal type of sinusitis. This is, indeed, what we now call *allergic sinusitis;* and if we would substitute this term for catarrhal sinusitis in Professor Hirsch's classification, we would bring it up to date. For we now speak of two types of sinusitis, the suppurative and the allergic. Of course there may be a combination of the two, as when infection is superimposed on an allergic membrane.

In suppurative sinus disease the process is usually confined to one sinus or one side of the nose. In allergic sinusitis, on the other hand, the involvement of the sinuses is usually symmetrical, resulting in a pansinusitis, because allergy of the sinuses is just a part of allergy of the respiratory system. Here the sinus mucosa exhibits the same reaction as the nasal

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mucosa, or the mucous membrane of the lower respiratory tract, and the process in the sinuses must be considered as only one part of the whole.

The symptoms of allergic sinusitis are well known to all allergists. I have never come across a better description of this condition than the one given by Joseph Beck[2] in the pre-allergy days, who referred to it as *hyperplastic rhinosinusitis*. "Clinically the patients present themselves with a definite history of nasal obstruction, especially in the upper straits of the nose, attacks of sneezing from five to twenty-five times in succession, followed by a diffuse watery discharge, etc., requiring the use of three or four handkerchiefs. These patients invariably complain about their eyes, and headache is rarely ever wanting, not only headache, but actual neuralgic pains about the head and face. The sense of smell is affected and in most instances it is absent or noticeably deficient. The examination is definite and striking, in that the nose is crowded with pale, waterlogged, thick mucous membrane. Invariably there are polypi present of variable size, in some instances so large as to protrude externally through the anterior naris, and posteriorly through the nasal pharynx. One of the most frequent associated general conditions, and not yet well understood, is bronchial asthma." In the light of our hindsight, we wonder nowadays why the relationship between such a nasal disorder and bronchial asthma remained obscure for so long a time. We now know that the underlying cause of such a syndrome is an allergic mucous membrane in the nose and paranasal sinuses.[7]

The course of the nasal disturbance will also help to identify the underlying pathology. In allergic sinusitis the mucous membrane of the sinuses is reacting to an allergen in exactly the same way that the nasal mucous membrane reacts—in other words, the process in the sinuses is but a part of the process affecting the upper, and in some instances the lower, respiratory tract. The secretions of both the nose and the sinuses will show eosinophil cells during the active stage of an allergic disturbance, and tissue sections show similar changes in any part of the respiratory tract. Edema of the submucosa and eosinophilic infiltration are the outstanding features. Everywhere the surface epithelium will be found to be intact, and the cilia quite normal. As Semonov[16] has recently pointed out, our attention has been focused on the activity of the nasal cilia for a good many years, but the important changes in allergy occur in the submucosa. It is the edema of the submucosa that is chiefly responsible for the symptoms and objective findings in allergic sinusitis, and the current interest in collagen diseases may throw more light on the mechanism of this edema. Robison[15] believes that tissue pressure is the key to the development of edema, and that swelling first occurs in tissues having the least tissue pressure. This helps to explain the vulnerability of the maxillary sinus, which is usually the largest of the sinuses and therefore the one having the least tissue pressure.

In contrast to the symmetrical involvement of the sinuses in allergy,

suppurative sinusitis is usually confined to one sinus or to contiguous sinuses on the same side of the nose. If the ostium of the involved sinus becomes swollen, it may become sealed off from the nose and the sinsusitis then runs a course independent of the nasal cavity. Shambaugh[17] has pointed out that anaerobic organisms are usually responsible for pure infectious sinusitis. This is the type of case in which irrigation with a solution of penicillin results in a prompt cure of a maxillary sinusitis that has been present for months, or even years. The more stubborn cases which resist irrigation are generally cleared up with an antrotomy. A striking feature of these cases of suppurative sinusitis is that when they are cured they stay cured. This is not the case with allergic sinusitis, with or without infection. Here recurrence is the rule, and it is now generally recognized that the most common cause of chronicity in sinusitis is an allergic membrane of the nose and accessory sinuses. The diagnosis and treatment of the underlying allergy in these cases has resulted in a more rational approach to the problem of chronic sinusitis, with the gratifying experience of much happier patients.

The clinical term *sinobronchitis*, now in use, is a good one because it serves to emphasize the relationship between sinusitis and diseases of the chest. This relationship has long been recognized by both otolaryngologists and internists. Among the former, Dean[4] gave one of the earliest and most comprehensive reports on sinusitis in children. He emphasized the importance of the removal of infected tonsils and adenoids, and the proper control of dietary and environmental factors. However, it soon became apparent that there was a relatively large group of children with recurrent sinus disease which did not improve under this type of management. Richards[14] suggested the possibility that allergy played an important role in this group, and Hansel[9] confirmed this with clinical and cytologic studies. We now realize that a detailed history, repeated clinical observation, and cytologic studies are necessary to evaluate cases of sinus disease in children, and that with the proper control of the allergic cases a much larger number of children will be spared the crippling effects of chronic pulmonary disease such as chronic bronchitis and bronchiectasis. In my own practice I have no greater satisfaction than that derived from seeing these children recover from their sinusitis, and with it their tendency to recurring nasal and chest colds. Nor is there anything more distressing than to see a young adult in the early twenties whose repeated attacks of sinobronchitis during school days were largely ignored or treated symptomatically, and who finally appears in your office with irreversible changes in the sinuses and lungs. Even one such experience is enough to make us doubly vigilant in caring for young children with a stuffy nose, postnasal discharge, and a dry cough.

In the treatment of these children with sinobronchitis very often a few simple measures are sufficient to bring great relief. The control of the important inhalant factors such as feathers, animal danders, and house

dust, together with periodic injections of a good house dust extract according to the optimum dosage schedule, will suffice in many instances to bring about improvement in the allergic mucous membranes. Acute infections are usually readily controlled by the antibiotics, and I believe that penicillin is still the most useful of these. With the prompt arrest of acute infections and the reduction in the number of recurring attacks, there will be no serious interference with the normal development of the sinuses in the growing child. I believe that this has been an important factor in the development of chronic sinusitis in adult life, just as repeated attacks of otitis media in childhood, with inevitable disturbance of pneumatization of the mastoid bone, favor the occurrence of chronic ear disease later. Thanks to Dohlman,[5] Shambaugh, and others we now realize that allergy plays an important role in middle ear disease in infancy and childhood, and there is no doubt that it is equally important in the pathogenesis of sinusitis.

In summary, a consideration of the embryology and histology of the nasal sinuses is helpful in understanding the relationship of pathology in the sinuses to bronchopulmonary disease. This is particularly well exemplified in allergy, where the outstanding features of edema of the submucosa together with eosinophilic infiltration are essentially the same in both the upper and the lower respiratory tract. Allergic sinusitis has always been with us, but in the past it has paraded under different names such as *catarrhal sinusitis* and *hyperplastic sinusitis.* Since allergic involvement of the nasal sinuses frequently begins in childhood, it is especially important to be vigilant in treating these early manifestations of respiratory allergy, in order to prevent the later development of chronic bronchopulmonary disease.

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806 May Building

MOLD'S CULTURE BY DIALYSIS

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PREPARATION of air mold extracts has always been based in the culture of them in solid or liquid media, mainly the latter.

As the culture becomes imbibed with the media there always remains a small quantity combined, so to avoid an intimate contact between them we have separated both by means of a cellulose membrane.

Before inoculation

After full growing

Cellulose tubes (not too absorbent) filled with the media were autoclaved and hung inside a 1000 ml Erlenmeyer flask, cotton stopped.

Inoculation is made by putting some spores on the surface of the tube.

Growing is carried out normally around the tube. When there is sufficient growth, separation is easily done by means of a spatula.

This method is preferred when we wish to obtain extracts as free from media contaminants as possible. It also has the advantage that the pellicle can dry quicker. Another important advantage is that the extract made from the pellicles contains more allergenic material so that it has not diluted into the culture media.

The accompanying illustrations give a clearer understanding of the method.

ALLERGY AND INDUSTRY

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THE ever widening horizons of allergy and its relationships with industry challenge the imagination. So far as I know, there has been no summary of the ramifications of such a relationship. First of all, we are dealing with that most complex representative of all animal life, the human being, both in and around industry, and then with the nearly equally complex consideration of allergy itself.

It is believed that allergy with asthma as its manifestation was recognized and described as long ago as the Ebers Papyrus. The use of the word *allergy* as the term for hypersensitivity was apparently first used by Schmidt in 1909 writing concerning skin manifestations.[14] One writer estimates that about ten per cent of the population have allergies of one type or another.[29] Yet another writer estimates that everybody has the capacity to develop allergic states of some sort and that everybody does.[4] Now somewhere between these two extremes there is no doubt a field of reality.

There is an equally divergent point of view regarding the definition of allergy. The purist, for instance, is most demanding inclusively and exclusively concerning those conditions which he will accept as allergic in classification. The realist, recognizing the need for practical considerations, has been willing to accept a somewhat more flexible attitude. Since allergenic materials are not necessarily impurities in the concept of either group, I will not refer to the second group as impurists. I choose to cast my lot with the realists. So that there may be understanding between us, let me identify the concept of allergy with which we will be concerned throughout the remainder of this treatise. The typical allergic reaction is one in which an antigen calls forth the production of harmful specific antibodies called reagins. Upon subsequent exposure to the same antigen, the reagin unites with it in some physicochemical combination, with the liberation of a noxious substance thought by many to be histamine or histamine-like. The action of these substances on the tissue cells causes allergic symptoms. The site of liberation determines the type of symptoms: in the nose, hay fever; in the bronchi, asthma; and in the skin, dermatitis.[63] There are many other manifestations of allergic origin, some of which will be called to your attention.

In bronchial asthma pathologic changes are found in the bronchial mucosa and musculature surrounding the bronchioles. Edema of the bronchial mucosa results in bronchostenosis. Spasm of the bronchial musculature adds to the obstruction. Mucous plugs formed of thick, tenacious

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See page 797 for description of air filter.

material further increase the resultant obstruction. Dehydration often contributes to solidification of the bronchorhea.[63]

The pathological changes in urticaria take place in the cutis. There is a dilatation of the blood vessels and an increase in capillary permeability, producing edema and flushing.[63]

In contact dermatitis it is felt that the primary reaction is limited to the epidermis, with edema between the individual cells. This intraepidermal fluid or spongiosis eventually reaches the surface, with the formation of visible vesicles.[63]

A review of the literature reveals the list of offending materials to be exhaustingly long and constantly lengthening. In 1943 Sappington listed all occupations with organic dust exposure from such sources as textiles, flour, sugar, wood (Brazil wood, satinwood, teak, some mahoganies, cocobolo, and California redwood), leather, and feathers, all creating potential for irritation of skin and upper air passages.[59]

Sensitization dermatitis, known as contact eczema or allergic dermatitis, is due to repeated exposures to substances normally innocuous.[42] These substances are called skin sensitizers. The housewife, relying upon soap, soap powder, cleanser, and more recently upon the synthetic detergents to achieve approved standards of cleanliness, frequently finds herslf plagued by a stubborn dermatitis labeled by dermatologists "housewives' eczema."[18]

One group of dermatologists observe that "everything that approaches the skin should be suspect of being capable of sensitizing it and provoking clinical episodes."[4]

According to present concepts, few if any diseases are due to one simple, uncomplicated effect or to a single causal agent.[65] One study on eczematous hand conditions emphasizes the multiple etiologic factors that can be present and the synergistic interplay of contact fungus, pyogen, virus, and food allergy, and those of emotion, sweat, soap, and water.[58] Polysensitivity[28] plus the synergisms of barometric changes, physical factors, emotional upsets, infections, constipation, secretory disturbances, dietary deficiencies, and chemical irritations further compound and confuse a picture already complex.

Hippocrates recognized that anger and hostility influence the asthmatic paroxysm.[78] The great clinician Osler thought allergic phenomena to be largely if not entirely neurogenic. To account for the somatic manifestations of allergic patients one must assume that they are constitutionally predisposed to the disorders which they develop and that specific psychodynamics are operative in those who despite a similar conflict constellation enjoy perfect health or suffer from different psychosomatic afflictions.[77] Rothman and Walker conclude, however, that, "in cutaneous diseases whose allergic nature is definitely proved, such as eczematous type of contact dermatitis and acute urticaria, the interplay of allergic and emotional factors has not been demonstrated."[57]

Clinically patients suffering from allergic disorders can be divided into

three groups: (1) In a considerable number of patients the clinical manifestations are no doubt sufficiently accounted for by an inborn or acquired allergy, i.e., on an entirely organic basis. (2) There is a group of patients labeled allergic in whom no offending allergen can be traced by the usual diagnostic procedures. Positive psychiatric evidence in these cases indicates that in them emotional states lead to physiological changes which imitate and are to all appearances identical with those observed in allergic diseases proper. The term *para-asthma* has been suggested by Peshkin[46] for this group. (3) There are patients in whom evidence of both a specific hypersensitivity and specific emotional states exist and in whom owing to a clear correlation between emotional disturbances and clinical manifestations it must be assumed that the emotional disturbances act as a catalyst on a dormant allergic predisposition.[77]

The possible combinations of the factors known to us at present are seemingly endless. The daily addition of new allergenic materials through advancing technology compounds these possibilities. From all this one would suspect that the anticipation, evaluation, and management of cases of allergy might well require the curiosity of a Sherlock Holmes, the ingenuity of a Thomas Edison, the patience of a Diogenes, and the optimism of an idiot. In some cases this is indeed true. Fortunately, the solution in the majority of clinical manifestations of allergy is somewhat more readily achieved.

Certainly these factors must be kept in mind in the diagnosis of allergic states. It may be necessary to utilize varied and specialized techniques, laboratory and otherwise. The literature is rich with such information. Basically the diagnosis consists of recognition of the presence of an allergic syndrome, identification of the agent or agents producing the reaction, and proof of their role by recurrence of symptoms when the patient is re-exposed to these agents after remission upon withdrawal from them. Needless to say, the simpler the whole thing can be kept, the better for all concerned.

Industry concerns itself with allergic phenomena, when it is involved, in one of several ways. First, it must deal with the employe who, through allergic illness not in itself of industrial origin, is frequently absent from his work or who otherwise is rendered less effective in his work. Asthma, eczema, and hay fever are all well known examples of this group. Secondly, it must deal with the persons whose allergic illness and/or concomitants or complications are aggravated by, or are the result of, exposures experienced in the industry where employed. Under the workmen's compensation acts, as written or as interpreted in some states, such conditions are held to be compensable.

It has been known for many years that industrial workers become sensitized to dry antigenic substances which they inhale.[53] Among those cited are veterinarians, grooms, and cavalrymen who become sensitized to animal dander; millers and bakers to meal dust; apothecaries to ipecacuanha;

quinine factory workers to quinine; and coiffeurs, wigmakers, dealers in fur skins, and animal keepers to hair.[53]

Asthma has been reported in workers exposed to acrolein (from flaxseed;[67] agar;[11] ammonium persulfate;[76] birch;[10] boxwood;[10,34,56] camphor;[76] castor bean dust;[27,43,53] cedar wood;[10,60,64] chlorazene;[76] chlorine gas;[76] chromic acid vapor;[76] cold;[36] Congo hard wood;[44] cotton dust;[25,49] dry fir (Christmas) tree needles;[9] fluorine;[25] fumes from burning charcoal, kerosene, tobacco and wood;[76] grain smuts;[25] isoamyl alcohol;[76] kejaat wood dust;[44,45] mahogany;[10] mite-infested oats;[70] mite-infested wheat;[1] naphthalene;[76] neoarsphenamine and other arsenical mists;[76] orangewood;[10] paradichlorobenzene;[76] paraphenylenediamine;[69] pine;[10] sulfur dioxide;[25] tamarack;[10] western red cedar.[44]

Bree lists "dusts of any kind" among the precipitating causes of attacks of asthma.[7]

Respiratory allergies as well as allergic dermatitis of the contact type are found where there is manufacture of flour, grain inspection, sorting and conveying of grain,[76] et cetera. Mill dust allergens have been shown to come from the grains themselves, various pollens, smuts (infesting wheat, corn, rye, oats, barley, sorghum, and certain vegetables,[76]) common air molds, rusts, bacteria, and insects.[75] Smuts as well as the common air molds are responsible in part at least for some of the hay fever and asthmatic symptoms occurring between and after pollen seasons and for otherwise unaccountable exacerbations during the pollen seasons. Workers in dirty feed mills, which cut condemned grain for cattle consumption, frequently develop respiratory allergies.[76]

The organic material disseminated as fumes and particulate matter from the manufacture of linseed oil, lead pencils (cedar wood dust), cedar oil, castor oil, malt, paint, paper, stock feeds, and soybean products as well as the dusts from cotton gins, feed mills, flour mills, seed mills, sawmills, or where there is storage or handling of grains, are common causes of respiratory allergies.[76]

Rhinitis, asthma, headaches, weeping and cystalgia have been reported as allergic manifestations of workers exposed to cold in the freezing chambers in a meat-packing factory.[36]

Workers manipulating iroko wood have manifested acute coryza, headache, and pharyngitis as well as chest symptoms including retrosternal oppression, a feeling of constriction, dyspnea, and dry cough.[12] Another writer has listed conjunctivitis, sneezing, increased nasal secretions, dyspnea, bronchitis, and asthmatic and influenzal attacks as the most commonly seen manifestations of mucous membrane reaction to wood.[6]

Hypersensitiveness to cotton dust (husk) protein was found regularly present in cotton gin operatives who were suffering from respiratory disease.

Bagassosis is apparently an allergic pulmonary disturbance due to an antigen in bagasse.

Persistent cough and bronchospasm due to exposure to fumes of range oil is thought to be on an allergic basis.[8]

A baker invariably developed rhinitis and asthma when exposed to a proprietary containing agar.[11]

Nasal allergies have been traced to dusts from stored grain and hay, feed stores, cotton gins, and woodworking establishments.[50] Molds, fungus, insects, feathers (chicken, duck, goose), rabbit hair (angora yarn), goat (mohair), sheep (wool), guinea pigs, rats, horse and cattle dander, cat hair, dog dander, pyrethrum (insecticide), flaxseed and flaxseed meal, cottonseed, and cottonseed meal have been found as the sensitizing agent in nasal manifestations of allergic nature.

Skin sensitizers are quite common in industry either as those substances encountered in the pursuits of one's occupation through materials handled or encountered in the atmosphere as vapors or spray droplets—or they may be the materials used to cleanse the skin of soil accumulated on the job.[18]

Wampler in 1943 listed fifty-seven occupations with dermatological exposures to eleven groups of sensitizing substances.

1. Dye intermediates
2. Dyes
   a. Fur and hair
   b. Leather
   c. Fabric
3. Photo developers
4. Rubber accelerators and antioxidants
5. Soaps
6. Insecticides
7. Cosmetics
8. Oils
9. Resins
   a. Natural
   b. Synthetic
10. Coal tar and derivatives
11. Explosives

In addition, he listed thirteen woods and fifty-two plants as well as biologic (bacterial and fungus) sources of sensitization.[71]

Schwartz has written an excellent chapter on occupational dermatoses in war industries.[16]

Sappington in 1943 listed as prominent among dermatitis producers in industry, animal products, chocolate, cutting oils, dough, fruits, photographic developers, sugar, vanilla, and vegetable products.[59]

Today's list of skin sensitizers to be found in industry, most of which have been reported in the literature, are cement,[18] dyes,[18] chrome,[18,42] and other plating metals, animal hair,[18] cocoa,[18] perfumes,[18] resins,[18] soaps,[18] detergents,[18] asphalt,[18] lacquers,[18] formaldehyde,[18] quinine,[18] paraffin oil, torch oil (kerosene), kerosene,[26] mineral oil, benzol, dolomite, grease, potash, tar fumes, plastic spectacle frames, rubber finger cots, machine

oil, sterilizing solutions, fuel oil, rubber head bands, rubber gloves, mill dusts, agar,[11] ammonia,[41] iroko wood,[12] oiled steam blue steel, lime dust, sulphonated coolant, alkaline cleaner,[26] trichlorethylene, transformer oil mist,[26] urea formaldehyde, bleach, laundry soap, liniment, orange I (azodye),[17] azodyes,[17] citrus fruit (alkalinized orange and grapefruit pulp),[5] bamboo,[33] chinoid compounds,[33] cinnamon,[33] cinnamon oil,[33] cocobolo wood (dalbergia),[32] D.D.T.,[22,55] dye and sizing, lapachronon (Brazilian wood—Peroba da campos),[13] paraphenylenediamine,[69] potassium bichromate solution (blueprint),[42] rubber compounds (natural-synthetic), linseed,[52] sunflower seed,[52] T.N.T., essence of turpentine,[48] varnish remover,[48] streptomycin (nurses),[72] "caine" topical anesthetics, and others too numerous to list. Among the cleaning agents commonly used in industry are soap (which may contain resins, fatty acids, lanolin, or perfumes as sensitizing agents), kerosene,[26] gasoline, and other volatile solvents. It is amazing to note the frequency with which the use of costly and dangerously inflammable solvents for skin cleansing is tolerated by industry while the lesser cost of a safer skin cleansing agent is exhaustively scrutinized for economy's sake.[38]

An eczematous dermatitis, which if not caused by soap is at least aggravated by it, is seen frequently in dishwashers, hairdressers, bartenders, surgeons, nurses, and dentists.[18]

Somewhat less frequently, other manifestations of allergy are seen in which the sensitizing and activating substances have been traced to occupational sources. Various forms of eye, ear, nose and throat, gastrointestinal, and central nervous system syndromes are described in the literature.

Allergic deafness has been reported from grain mill dust, and another case from soybean dust in mill workers.[30]

A case of urticaria associated with cerebral edema in which a worker in the ammonia section of a chemical plant developed dermatitis on the dorsa of the hands and thereafter went through a bizarre symptom complex of a prolonged and disabling nature has been reported. It was the consensus of the neurologists, internists, and dermatologists that this case presented clinical evidence of cerebral accident due to allergens of unknown origin which were also responsible for the exfoliative dermatitis.[41]

Complications or concomitants of these occupational allergies are reported from time to time. Annadoun reports that spontaneous rib fracture from coughing is not infrequent in cases of bronchial asthma.[2]

Fatalities are reported as the result of severe occupational allergic reactions such as that sometimes seen from wasp stings.[74]

An additional group of concern to industry are those persons whose sensitivity is activated by medications or equipment used in the treatment or prevention of industrial injuries and illnesses, including allergic illness.

Well known to many of us are the medicamentosal reactions to mercurial antiseptics, ointments, soak solutions, et cetera. With the less frequent use of these materials reactions are being seen to the other or more frequently

used medicaments. Among these are agar; antipyrine[37]; arsenic; antimony; aspirin;[38] bromides; barbiturates; belladonna; bismuth; chloralamide; copaiba; cortisone;[6] cubebs; chloral; chloral hydrate; chrysarobin; ergot; hyoscyamus; iodides; ipecac; mercury; morphine; opiates; phenacetin; phenobarbital; phenolphthalein; pilocarpine; potassium chlorate; quinine; plastic rimmed safety goggles; salicylates; sulfa drugs; protective creams; rubber or plastic finger cots, mittens,[67] gloves, and aprons;[26] silver nitrate; pontocaine[30] and other "caine"-containing medicaments; turpentine; zinc sulfate,[73] et cetera, which have been found responsible for various skin manifestations such as erythemas (papular, macular and patchy, morbilliform, scarletiniform); exfoliative dermatitis (secondary erythroderma); fixed drug eruption;[37] urticarial, vesicular, herpetic, bullous, polymorphous (erythema multiform type) eruptions; pustular (acneform, ulcerative, condylomatous or anthracoid, gangrenous), purpuric and petechial, keratotic and pigmented eruptions.[73] Some of these terminated fatally. Others were complicated by hepatitis and epididymitis.[37] Transfusions have produced gastrointestinal allergy;[23] aspirin, severe histaminic shock;[38] antirabies vaccine, neuroparalytic accident;[31] zinc sulfate, allergic eye reactions.[73] Antihistamines have been credited with producing acute urticaria, dermatitis,[19] and angioneurotic edema.[21]

Not infrequently seen are the prompt and delayed allergic manifestations of animal serum sensitivity following administration of antitetanus serum. The increased use of the toxoid—along with the now common practice of skin testing before use of the antisera—is reducing the frequency of these reactions. Myocardial infarction has been reported following the administration of tetanus antitoxin.

The relatively new and constantly growing group of antibiotics has opened an entirely new field of high potential allergenic substances. The literature is rich with reports of sensitivity reactions to penicillin, bacitracin, chloromycetin, aureomycin, and others. Some of the manifestations described are severe serum sickness type,[79] genital dermatitis,[39] genitocrural pruritus,[54] contact dermatitis,[69] atopic dermatitis, and angioneurotic edema. Studies are said to have shown 5 per cent of athlete's foot hosts to be penicillin-sensitive.

Equally involving are those undesirable reactions not of an allergic nature resulting from the use of medications in the treatment of occupational allergic disorders. The antihistamines have been found responsible for agranulocytosis,[55,62] hematuria,[40] impotence,[24] and tachycardia.[51] Suicide has been reported following cortisone therapy.[6]

Multiple chemotherapeutic remedies thought to be synergistic may manifest antagonistic allergic cutaneous responses. Toxic reactions from the concomitant use of antibiotics, para-aminobenzoic acid derivatives (i.e., procaine, pontocaine, larocaine, butyn, benzocaine, monocaine, and tutocaine) and sulfonamides have been reported.[20]

An employer's increased costs through occupational allergy are usually

reflected in the cost to the purchaser. These increased costs arise through loss in manpower and decreased production due to rapid turnover, employe grievances, and lower morale—and in huge compensation costs.[18]

The future, however, is not so bright for the worker who has developed an occupational allergy. Until recovered sufficiently to return to work, often a matter of months, particularly in dermatitis cases, he must support his family on the compensation check he receives each week in place of his usual weekly pay check of double or triple the amount. This may necessitate an appeal for welfare assistance for the large family dependent on these earnings. The story does not end here, however, nor does it end after the discomfort, annoyance, and inconvenience of the symptoms have subsided. Even after symptomatic recovery any further contact with the original antigen will provoke a relapse and further suffering and loss of earnings. Moreover, other substances encountered daily in the normal course of our lives easily become antigens to the sensitized person. Finally the worker may be forced to leave the type of work for which he has spent years (and his employer countless dollars) in preparation and seek work in another field where he is not exposed to the offending materials—but where he may be doomed to lower earning capacity for the rest of his life. One facet of the problem can perhaps never be solved: namely, that of the frequency with which industrial raw materials prove to be antigens to an apparently normal person.[18]

PREVENTION

The treatment of these occupational allergies is twofold. The first, which is the hallmark of all industrial medicine, is prevention. Prevention of occupational allergy may call for use of any or all of the following:

A. Environmental control.—

1. Control of manufacturing processes to minimize the presence of free materials outside of machines. This control would include supplemental equipment which collects, exhausts, or dilutes (ventilation) atmospheric contaminants.
2. Improvement of manufacturing processes, minimizing the need for human contact with the materials being dealt with.
3. Substitution of materials of low allergenic potential wherever possible for those known to be sources of trouble and not readily controlled as above suggested.

B. Personnel.—Selective placement of personnel, by history, physical characteristics, and in some cases sensitivity tests, who are least likely to develop sensitizations. This handling, to be practical, would perhaps best be thought of only when dealing with processes or materials known or, with good reason, thought to be of unusually high sensitivity producing potential.

C. Personnel Protection.—Provision of personal protective materials and equipment.

1. Materials such as laving solutions or barrier creams which prevent contact with, or dilute, reduce, oxidize, or otherwise neutralize the offending materials.[51]

2. Clothing, masks, gloves, and/or other apparel.

(Of course, in addition to making such materials available, measures must be taken to see that they are used. Perhaps the best method is through education.)

3. Frequent bathing or washing with a cleansing agent that has been proven safe and provided by the employer—and supervision must prohibit the use of other skin cleansing agents which are known to be dangerous.[18]

4. Rotation of personnel to provide rest periods from contact with the offending materials.[78]

TREATMENT

The second, active treatment for existing allergic manifestations is largely predicated by the acuity or severity of the disease and the personal preferences of the attending physician. It includes such materials as the following:

1. Epinephrine—topically, as an aerosol, or parenterally. Sensitization and intolerance to epinephrine have been shown.

2. The sympathomimetics such as ephedrine, aminophylline and the amphetamines.

3. The antihistamines. It should be remembered that the antihistamines do not operate as true antianaphylactics.[21] In fact, there is some reason to believe that histamine is an end product of the reactive phenomena—if this be true, then early therapy may prevent the formation of histamine bodies, rendering the use of antihistaminics unnecessary and possibly undesirable. They may relieve, but not predictably, mild atopic dermatitis, contact dermatitis, serum reactions, gastrointestinal allergy, and atopic reactions to drugs, such as urticaria from aspirin. Antihistamines can be used in conjunction with sympathomimetic agents.[66]

4. The use of topical medications in general is to be discouraged. Whenever necessary for excessive weeping of skin surfaces or persistent pruritus, such medication should be confined to simple materials known not to produce undesirable skin reactions themselves. Their use may compound or completely change for the worse the abnormal conditions already present. Starch baths or astringent baths such as Burow's solution may prove useful in certain cases. Some of the urticarial lesions in which relatively small amounts of body surfaces are involved may respond favorably to calamine lotion (with or without phenol), antihistaminic or anesthetic lotions, creams, or ointments used sparingly and for short periods of time.

5. Sedatives as symptoms demand. "Morphine is used, apparently, far

too frequently" according to H. L. Alexander.[3] "It is an illogical drug for asthmatics since it has been shown to induce bronchospasm. Several deaths have been attributed to morphine and it should never be used."

6. Planned desensitization is rarely practical, but spontaneous desensitization occurs commonly.[51]

7. Any combination of the above.

It should be borne in mind that promiscuous medication is to be discouraged for among other reasons those undesirable reactions which may occur as previously discussed.

The third group with which industry is concerned in matters allergic are those persons of the community surrounding the industry who are able to trace the source of their torment to the industry.

Wyman in 1872 observed that among the most prominent causes of a paroxysm of autumnal catarrh is the dust and smoke of a railway train.[14]

An example of endemic asthma is reported in which persons who worked in a castor oil factory or who were within a mile of it were sensitized to the castor bean dust ejected from the chimneys. A large group of children in a school opposite the factory were affected. Housewives and children had their attacks at any time during the day or night. Sensitized persons living in this vicinity but working elsewhere had their attacks only at night, on returning to their homes.[15]

Twenty-four per cent of the patients seen by an allergist in Minneapolis have been found to have respiratory allergies chiefly due to grain smut sensitivity. Among the patients affected are clerks and stenographers within the loop district of Minneapolis, which is only eight blocks from the milling district.[76]

Insecticides sprayed on orchard acreage from airplanes have not only aggravated the symptoms of asthmatic patients but have also been shown to cause asthma in some cases.[76]

Phillips reports a group of allergic persons who were exposed in successive years to the pollen of sugar beets, which they had never before encountered. Within four years after this plant was introduced a considerable number of individuals who were never previously sensitive to sugar beet pollen began to develop such sensitivity.[47]

Truitt reports mushroom flies descending on the neighborhoods of the mushroom houses in clouds to annoy everyone and to make certain susceptible people wheeze.[68]

The exact nature of the allergenic components of the organic dusts to be found in smogs requires clarification.[76] It seems reasonable to suppose that reaction between chemical components of the smogs may produce conjugate materials of allergenic properties. These reactions undoubtedly vary with temperature, humidity, concentration of the components, catalytic materials, et cetera, to such degree that no reasonable anticipation of quality or quantity of end product can be assumed.

Lastly and briefly, industry is concerned with the allergic response created by its products in the consumer. This is perhaps the largest group of all, since it includes all of those previously discussed and many others. There is presently no estimation of the number of people and substances that are or could be involved. Such reactions to kapok, orris root, detergent compounds used in laundry, kitchen and bath,[18] nylon hair nets, nylon hose, dress dyes and dress shields,[42] and others are commonly known to all of us. Some of the interesting but less commonly seen sources of sensitization are polyethylene glycols (carbowaxes), cocobolo wooden cutlery handles, white gold spectacle frames, plastic spectacle frames, and certain plastics. Allergy to acrylic dentures has been reported. Optic neuritis has been traced as an allergic response to cold permanent wave.

It seems safe to speculate that the location, operation, and product of an industry might in the final analysis depend a great deal upon the temperament, type and severity of reaction, and most of all the number, of the people involved in the allergic response.

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ALLERGIC PROBLEMS IN MODERN INDUSTRY

Prevention and Control

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WITH the phenomenal growth of the chemical industry in this country and the introduction of new chemical substances into all types of fabrication processes, the medical community has become increasingly aware of the many toxicological problems which may arise in industrial work. A common cutaneous hazard to which workers may be exposed is that of sensitization. This paper is devoted to a discussion of how allergic problems in industry, especially those which affect the skin, may be avoided and controlled.

Experience has taught industry that whenever it contemplates the introduction of a chemical substance into a process, it is economically and socially advisable to determine the toxicological properties of the new substance and to ascertain whether it will irritate or sensitize the skin. For example, if an industry plans to market or use a new stabilizer for plastics, introduce a new coolant, or add a new component to a cutting oil formulation, it is imperative that an evaluation for the potential irritation or sensitization effects of the new substance be made prior to its introduction. There are several methods which may be employed to ascertain the sensitizing capacity or potential allergenicity of a given chemical compound. We shall discuss briefly the use of the methods, their advantages, and their limitations.

GUINEA PIG TECHNIQUE

Based upon animal experiments conducted by Landsteiner and Jacobs, and Landsteiner and Chase, several investigators[2] use a method of evaluation in which repeated standard doses of the compound are administered intracutaneously to guinea pigs every other day for ten doses; following a rest period of ten days, a challenging or test dose is again administered intracutaneously. Determination of sensitization is made by comparing the reactions observed following the test dose to those observed during the sensitization period. If the values of the test or challenging dose readings are appreciably higher than those of the initial readings, the compound can be said to have produced sensitization.

Unfortunately, this method has only a limited usefulness. The reasons for its limitations may be sought in observations that:

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1. Guinea pig strains are not uniformly susceptible.

2. The skin of the guinea pig is probably less easily sensitized than that of man.

3. The histopathological changes in the guinea pig are not identical with eczematous contact sensitization of human skin.

4. Immunologically the induced guinea pig sensitization may be quite different from that in human sensitization.

5. A routine method which employs a uniform sensitization schedule, a uniform test dose, and a uniform incubation period does not take into account that chemical substances may differ markedly in their threshold sensitizing dose, the time required to sensitize the skin, and the test concentration which will evoke a hypersensitivity reaction.

It is most likely that because of the latter this method fails to detect many sensitizing agents. The guinea pig test, however, has some usefulness when employed to screen out potent eczematogenous substances, and it may be used to avoid the use of such potent sensitizers in subsequent human skin testing.

PATCH TEST TECHNIQUE

Following the use of the guinea pig screening test, the substance or compound can be appraised with the help of a repetitive patch test procedure. Most dermatologists, allergists, and hygienists who are interested in cutaneous irritation or sensitization produced by consumer goods or industrial materials, are familiar with the "prophetic" patch procedure. The method recommended by Schwartz and Peck[8] consists of two series of patch tests performed on the same individual ten to fourteen days apart. In the first series, reactions are considered to be due to primary irritation. Reactions in the second series alone are considered as evidence of sensitization due to exposure to the first series of applications. In our experience the human patch test is much more informative than the guinea pig method for determining the sensitizing potential of human skin.

In planning the repetitive patch evaluation an attempt should be made to approximate usage conditions as closely as possible. The limitation of the patch test in this connection is that a test covers a relatively small cutaneous area and cannot simulate the extensive areas exposed in some usage conditions. Single patch exposures for twenty-four to forty-eight hours may be insufficient to induce sensitization which may be produced readily by continuous usage exposure. Exposure for three to four days may therefore be necessary. The manner of application may vary with the physical state of the substance: whether or not it is a primary irritant in usage concentrations; the total formulation of which it is only a part; the manner of its use in production, e.g., continuous, intermittent, concentration in usage, or type of industrial process. The amount of useful information which may be obtained from a repetitive patch evaluation depends upon how closely the test conditions resemble the industrial exposure.

STATISTICAL CONSIDERATIONS IN THE REPETITIVE PATCH TEST

In any test in which the results are to be applied to the general population, it is probably wise to ask the statistician several questions.[3,4] How many subjects is it necessary to test in order to predict that a rate of positive reaction in the general population lies within certain limits? With what certainty can the prediction be made? Although the reaction rate is zero in the experimental or test group, what might the probable incidence of reactions be in a large segment of the general population?

To understand the importance of adequate size of a test group, the enlightening figures of Henderson and Riley can be used as a guide. They demonstrate positive reaction rates in a large population based upon numbers of positive results in test groups of various sizes. While it is true that the number of allowable reactions prior to release in a community of a designated substance depends upon the manner of use of this substance, and its value to the community, nevertheless it can be shown that a considerable number of individuals must be tested to obtain statistically valid information about the sensitizing capacity of a substance under investigation.

One would be reluctant to pronounce a substance innocuous for a large number of users on the basis of no reactions among 100 subjects. There would be a 95 per cent likelihood that the frequency of reactions in the general population will not exceed 3 per cent. If the sampling is 200, it would be just as likely that the reaction rate would not exceed 1.5 per cent. The work of Henderson and Riley clearly demonstrates the need of large subject samples when reaction rates are zero, one or two per sample in order to predict most likely reaction rates in a large population.

INTERPRETATION OF PATCH TEST RESULTS

When no positive reactions to the second test or the challenging exposure are observed, one cannot be certain because of another consideration that the potential allergenicity of the substance in question is nil or very low for the actual consumer or industrial worker. In any patch test assay the conditions may not even closely simulate consumer or industrial exposure. The artificial conditions may therefore account for the lack of reactions.

The results of the repetitive patch test, as with many other bioassay methods, are influenced greatly by variables which are, even in the best hands, almost uncontrollable. Such factors as temperature, humidity, personal habits of the subject, and perspiration may enhance test reactions. The results will only indicate the relative sensitizing capacity of a substance under the specific conditions of the test.

Nonetheless, the repetitive or "prophetic" test is a very useful bioassay method. It helps in the detection of sensitizing substances among potential or already used industrial materials. It provides a means of determining

whether or not a new material may be released for limited, controlled, or general use in industry. It is recommended that the test be run in conjunction with usage tests.

USAGE TESTS

The type of test which provides the most valid kind of information insofar as potential allergenicity is concerned is the usage test. When a substance has been shown to evoke few or no reactions by the repetitive patch technique in a test group which is statistically adequate, the final determination as to whether or not it can be used safely in industry is by a small-scale trial. During the trial usage period the workers in the test group must be observed periodically for untoward reactions. If the patch test results indicate a moderate or high sensitizing index, it may be necessary to employ a planned hygienic program during the controlled usage test. If reactions during the usage trial are negligible over a prolonged period, the material may be marketed for general or industrial use.

Outbreaks of eczematous contact dermatitis which have occurred because a new material was not investigated at all, or investigated inadequately, are common. Reports are not published generally and medical information concerning the cutaneous hazard are frequently not discussed outside the affected industry.

A report of Dr. J. M. Lynch[5] concerned with the dermatitis-producing qualities of a new coolant may serve as an example of what may sometimes occur when preliminary studies are not carried out. During the year following its introduction in one plant fifteen cases of dermatitis of the hands and forearms were reported. The manufacturer of the coolant revealed the nature of six of the eight components. The six known components were nonirritating and nonsensitizing in the concentration used. The remaining two components were not identified. Each of the known components failed to evoke cutaneous reactions when eight of the fifteen affected workers were patch tested. The freshly diluted coolant and used coolant evoked reactions in five of the eight workers. These cases averaged fourteen visits to the plant clinic, and the average duration of the disease was five and one half weeks. Six of the fifteen cases had to be transferred because of their dermatitis; two of these returned to exposure unsuccessfully; in four persons the dermatitis cleared while they remained exposed, demonstrating "hardening," and five others were transferred for nonmedical reasons to an insoluble cutting oil operation. In this particular outbreak the dermatitis was not disabling but the number of prolonged cases of dermatitis of the hands caused some alarm. The problem could have been avoided if preliminary patch and trial usage evaluations had been done.

In industry a new chemical substance with special properties may be developed which is irritating or sensitizing or both. There may be no available substitute or the compound may be an intermediate which is encountered in only one part of a chemical synthesis. This is a common

problem and requires the introduction of a hygienic program to prevent possible contact. Such measures are imperative in the manufacture of explosives such as tetryl and T.N.T.; in operations involving the manufacture of certain plastics; in the use of plasticizers, dye intermediates, rubber antioxidants, accelerators, and mildewproofing agents; and in handling nickel, chromium and many other valuable industrial substances.

PREVENTIVE PROGRAM

A hygienic program for the safeguarding of an operation which employs a sensitizer or irritant should include several major considerations:

(1) Safety engineering measures; (2) Protective measures used by the individual worker; (3) The role of an industrial medical department in the hazard control program.

The most effective way to prevent exposure is to enclose the entire process involving the hazardous compound. The entire production, fabrication machinery or equipment may be enclosed from the point at which the raw materials are introduced to the finished product. More often than not, however, for technical or economic reasons, complete enclosure is not feasible. If complete enclosure is not possible a hygienic program must be instituted so that the worker has minimal contact with the sensitizing material by spillage, handling, and exposure to vapors and dusts. A maximum of effective external devices must be used for this purpose. These include guards against splashing of liquids, and suction ventilating equipment for fumes or dusts. The manner in which the worker handles the hazardous material is a major factor in minimizing contact; hence, the work habits are of prime importance. Expert guidance for and supervision of the worker is frequently required to help establish nonhazardous handling.

Good plant housekeeping is the keystone of prevention. This involves the cleanliness of the operations area, and of the equipment and tools used in the particular process, as well as cleanliness in the rest of the plant. It includes effective ventilation of the factory building in order to prevent the settling of dusts and concentration of fumes which may contain the sensitizing substance. In modern industry there is no legitimate excuse for a dirty, untidy plant.

Insofar as the involved operator himself is concerned, the most effective control measure is that *he have a complete understanding of the safety program in which he plays a key role.* He must have available adequate washing facilities which he may use as often as is necessary for effective hygiene. He should be instructed to use the showers at the end of his shift. The employer must provide locker room facilities for changing clothes, as well as effective detergents and clean towels. In operations in which the work clothes become quickly contaminated with a sensitizer or irritant, it is a good hygienic policy to have the employer supply clean

work clothes and/or underwear each day, and to be responsible for the laundering of the soiled clothes.

The effectiveness of the cleanser is an important consideration. The type of cleanser will depend essentially upon the properties of the substance which has to be removed from the skin. Generally a neutral toilet soap to which a synthetic surface active agent has been added will suffice. Nonirritating scrubbers may be added if greases must be removed from the skin.

The protective clothing which may be indicated in a particular operation may vary from complete body protection with an impervious material to simply covering one area such as the hands, when gloves are used. The type of material used for protective apparel will again depend upon the substance to be avoided.

A much-sought-after means of avoiding chemical contact with the skin is the so-called protective ointment or barrier cream. Dr. Louis Schwartz[9] has described at least six types of protective ointments. These mixtures theoretically act as a barrier through which the sensitizer or irritant does not penetrate. Several enthusiastic reports have come from a few sources about the efficacy of certain barrier creams. We cannot share this enthusiasm. In our opinion, the notable benefits which are derived from the use of those barrier ointments available to date are due to the increased frequency and number of washings. The skin is washed systematically before each fresh layer of ointment is applied, when the worker goes to lunch and at the end of the shift. This may mean that a thorough skin cleansing is carried out two to six times per day. Hence, the sensitizing and irritant agents which accumulate on the skin are washed off more frequently and have less opportunity or time to cause cutaneous reactions.

THE ROLE OF THE MEDICAL DEPARTMENT AND CONSULTANTS

In choosing workers for a job which involves exposure to a sensitizing substance, it is important to avoid assigning persons to such operations who have (1) recurrent eczematous contact dermatitis from other industrial contactants, (2) seborrheic dermatitis, (3) dermatophytosis with an "id" reaction, (4) stasis syndrome, (5) icthyosis, (6) pompholyx, (7) other skin problems which result in itching and scratching.

The medical consultant must periodically examine workers exposed to a sensitizer for possible cutaneous or other symptoms. If an outbreak occurs several weeks or months after the introduction of the new material, it is imperative to determine whether the new substance is responsible for the outbreak, and if so what the deficiencies in the hygienic program may be. Following treatment of these affected workers, if return to the same exposure is followed by a recurrence, it is wise to have the sensitized employe transferred to other work. The medical personnel in an industrial organization assumes the responsibility, with expert counsel if necessary,

to guide the hygienic program, check on its effectiveness, and make periodic recommendations for revision of the safeguards when necessary.

THE INVESTIGATION OF ALLERGIC CUTANEOUS PROBLEMS IN INDUSTRY

The general purposes of an investigation of an outbreak of dermatitis are: (1) To study clinically the cases of dermatitis which have occurred in an industry. (2) To study in detail the operations and the plant conditions in which the affected workers are employed. (3) To determine what factors are responsible for the outbreak of dermatitis and to determine the hazardous exposure to the incriminated sensitizer or irritant in each operation. (4) To determine what hygienic measures may be taken to make possible the continued use of a sensitizing or irritant material for which there is no substitute.

These are in essence the principles of any industrial hygiene survey and apply to irritants, sensitizers, and substances which have toxic effects on other organ systems.

The effectiveness of a study of a cutaneous problem in industry depends upon a number of factors. Of great importance is the unrestricted cooperation of management and especially its help in obtaining the necessary facts and figures concerning the industrial operation in which the outbreak has occurred. These facts must include the nature of the exposure, substances involved, how long they have been used, number of cases, and the duration of the total problem. It is frequently necessary to make inquiries of other manufacturers who supply either the raw materials or the finished products to the affected industry. The facts about plant operation and materials, number of workers exposed and affected, may be obtained from the plant production manager and the medical history of each affected worker from the medical department. It is sometimes necessary to convince management that a thoroughgoing and critical examination of production methods, as well as of the medical aspects of the problems, is necessary to solve the problem and that such a study is of benefit to both workers and management.

The affected workers should be questioned individually and examined carefully. Depending upon the particular problem, it may be advisable to examine not only the workers who have reported their medical problem but all workers handling the same suspected compound. Some workers are reluctant to report medical complaints, and the real incidence of occupational disease may be determined only by examination of all of the exposed employes.

The consultant—dermatologist or allergist—must become familiar with the industrial processes in which the outbreak has occurred. This can be done only by going through the plant with a foreman or production superintendent who is familiar with what each worker does. The consultant should consider carefully the safety engineering methods which are

employed, their apparent effectiveness, the condition of the machines and tools, the cleanliness of the plant, the protective measures used by the individual, his hygienic habits, and the facilities for washing. In the survey he must evaluate the numerous opportunities for possible cutaneous contact. These opportunities may be afforded by a combination of conditions such as:

(a) Hazardous nature of the industrial operation

(b) Careless working habits of the employe

(c) Inadequate guidance of employes in work procedures

(d) Inadequate system of protection against contact with the sensitizers.

Significant factors which were discussed previously under the planning of a hygienic program for the handling of a sensitizer in industry, must be considered in the study of an outbreak. The questions to be answered are: how extensive is the exposure of those working with the suspected materials in an industrial process; what materials are suspected of causing the outbreak; what measures may be used to determine the etiologic agent(s)?

The first two questions may be answered by the survey; the last may be determined in several ways. Diagnostic patch tests may be done with all of the substances used by the affected workers. Their concentrations should be those which are employed in the industrial process unless such concentrations are known to be irritating. In that case an appropriate nonirritating dilution should be used. The patch test is a valuable diagnostic procedure but is strictly an aid and should be used as supportive evidence that the affected worker has or has not become sensitized to one or more substances in a particular occupational milieu. It is not always necessary to test to household and hobby contactants to which the worker is exposed as one must do in the diagnostic appraisal of an isolated case. If a particular formulation is incriminated, as in the case of solvents, fabric finishes, antimildew and waterproofing impregnated substances, cutting oils, and synthetic rubber, it is important to test each component individually as well as to the complete formulation.

It is well to examine for all the possible factors which may enhance sensitization. Commonly occurring conditions which increase the possibility of sensitization are concurrent primary irritation, abrasions, accumulation of material beneath the impervious protective apparel as in the case of perforated rubber gloves, and the presence of a surface active agent. The three last conditions may increase markedly the percutaneous absorption of some sensitizers. These factors alone may make for the appearance of cutaneous reactions.

It is important to question the affected worker about concomitant allergic and toxic symptoms which may not be referable to the skin but which

may be caused by the same exposure. In investigating a hazard, the dermatologist or allergist must consider the entire toxicologic picture. In some instances allergic reactions in more than one organ system may be produced; in other exposures the allergic problem may be relatively benign by comparison with the other toxic reactions. For example, the industrial exposure to the ethylene amine class of compounds with the general formula $NH_2RNHRNH_2$ is now known to cause a rather high incidence of dermatitis, many cases of which are of the sensitization type. Inhalation of vapors of this class of substance will give rise to asthma.[1] The intermediate oxidation products of p-phenylenediamine may give rise to eczematous dermatitis and true bronchial asthma.[7] Industrial exposure to such explosives as T.N.T. (impossible to avoid during World Wars I and II and continuously present) may result in hepatitis, aplastic anemia, hypochromic anemia, and cyanosis, as well as in eczematous sensitization.[6] Exposures to beryllium compounds may produce an eczematous contact dermatitis. Inhalation of the same compounds may give rise to an acute pneumonitis or, after an elapse of some time, chronic pulmonary granulomatosis.

CORRELATION OF CLINICAL STUDY AND PLANT SURVEY

From the clinical examination and observations made in the plant survey, it should be possible to determine the factors responsible for the outbreak of the dermatitis and to determine the potential hazards in each operation. The patch test studies may incriminate one or more substances as sensitizers. However, the opportunities for repeated or prolonged contact revealed by such a study are of utmost importance in determining what can be done to safeguard the use of a material in any particular industrial process.

In his recommendations, depending upon the nature of the problem, the consultant may suggest elimination of the sensitizing chemical material or component, or a complete program of control to make possible the continued use of the substance with a minimum of hazard to the worker.

The fields of industrial dermatology and allergy have become as complex as the American industrial scene itself. Cutaneous and allergic problems which arise in industry cannot be solved by physicians whose experience is limited to clinical practice. Their prevention and control requires the joint experience of trained personnel in industrial hygiene, toxicology, chemistry, dermatology, and allergy. Several teams of trained personnel from university and government toxicologic research laboratories are now active in this field. The number of such teams is still meager by comparison to the expanding requirements of industry.

We trust that, with the growing recognition of the role which such investigative groups play in the maintenance of the public health, their number and the use of their services will increase.

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LIFE EXPECTANCY

In a Thanksgiving message at New York City, Dr. Louis H. Bauer, president of the American Medical Association, said that "the length of human life in the United States has doubled—for Americans as a whole since our nation was founded and for the industrial population within just the past seventy-five years."

Dr. Bauer announced that in recognition of this achievement the World Medical Association, of which he is secretary-general, is calling its first western hemisphere conference. The event will be held in Richmond, Virginia, from April 23 to 25, 1953.

"Medical leaders from the American republics and United States practitioners and specialists will share existing knowledge of how life can be made longer and healthier," he said. "Together they will explore new medical horizons that hold the promise of further advance."

"Good living conditions and good medical care have wiped out the differential that as recently as 40 years ago meant a briefer life by some half dozen years for the wage-earner than for other Americans," Dr. Bauer commented.

"If medical gains continue at their present pace, life expectancy in this country will reach and even pass seventy years well before the end of the present decade. Moreover, life at any age will be freer of disability and pain for more people than ever in the past. Surely this is reason for giving thanks and for exchanging medical knowledge among the doctors of the world."

Meeting jointly with the World Medical Association at the western hemisphere conference will be the Pan American Medical Confederation of which Dr. Jose Angel Bustamante of Havana, Cuba, is president. Leaders of national medical societies making up these groups are expected at the Richmond meeting, along with speakers representing the nineteen recognized medical specialties and the field of general practice. Dr. Bauer will act as moderator.

EVALUATION OF INDUSTRIAL DERMATITIS BY ANALYZING ITS PATTERN

GEORGE L. WALDBOTT, M.D., F.A.C.A.
Detroit, Michigan

IN deciding whether or not a dermatitis is due to occupational causes, we are liable to make serious errors in judgment. For instance, the fact that a person is continuously exposed at work to a highly active sensitizer does not eliminate the possibility that finger nail polish, hair dye, or a cold cream may be the source of his dermatitis. When we detect fungi and bacteria in smears or cultures from a certain lesion, we are not necessarily dealing with a primary infectious source or a mycosis of the skin coincident with the patient's working condition; the lesion may be an industrial dermatitis with a secondary bacterial or fungous infection superimposed on it. In another instance in which sensitivity to multiple sources exists, strongly positive patch test reactions may be obtained to cosmetics, lesser ones to the items with which the patient has contact at work. This again leads to confusion, and makes us inclined to rule out the occupational causes. In other cases, an occupational agent which does cause the lesion may give a negative patch test; this may wrongly lead us to exclude its consideration as a major cause. All these examples indicate that good judgment and experience are required to properly interpret our observations.

In the past, there were only two principal means of detecting the causes of a contact dermatitis, history taking and patch testing. It is the purpose of this paper to show how the analysis of the pattern of a lesion can be a most valuable aid in the appraisal of an industrial lesion. I shall not review our studies[2] on classifying patterns of contact dermatitis; this is fully covered in my book on contact dermatitis.[1] Instead, I should like to demonstrate by means of typical cases how the study of a pattern can solve the problem at hand.

At a large dermatological university hospital in Europe, I was shown a case of dermatitis of the face which was considered to be due to a plastic dust with which the patient had contact at work. Several other individuals from that plant were in the hospital with similar lesions, distributed on the hands, wrists, and face. In this case, the lesion extended to an area around the temples, the top of the earlobes, and the forehead. Furthermore, the most intense irritation was localized at a semicircular area of the neck and the upper portion of the chest. Had the plastic dust been responsible for the lesion, the v-shaped outline of the patient's dress would have demarcated the lesion. The irritation about the patient's ears

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Approved for publication.

and temples suggested a hair cosmetic. Upon letting her hair down in front of her face, the end of the hair touched the skin exactly on the area where the eruption showed its greatest intensity. Only hair rinse could have been responsible for this lesion. This was verified by patch tests.

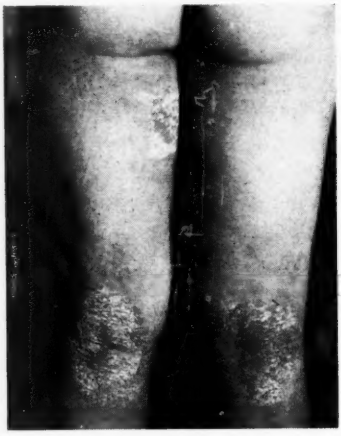

Fig. 1.

A dermatitis on the buttucks of a truck driver was considered to be due to the plastic of a toilet seat. In studying the pattern of this lesion (Fig. 1), it became apparent that the distribution did not fit that of a toilet seat dermatitis. The latter produces a semicircular lesion with a wider radius on the buttocks corresponding in size to the outline of a toilet seat. This lesion was smaller in size and located more centrally. It was associated with an area of dermatitis on the flexor surface of the knees. This observation and the fact that the patient was a truck driver soon established that the leather dye of a new leather seat cover in his truck was responsible for the lesion. The patchy appearance and predominance of the lesion on the left side was due to the patient's habit of sitting on one side, and further, to friction and perspiration in that region. The eruption behind the knee suggested an atopic lesion. However, it proved to be due to contact with the leather cushion which protruded from the seat. When he perspired, the dye had permeated the patient's thin overalls. This was, therefore, an occupational and compensable lesion.

Several interesting instances* of contact dermatitis of the hands have been observed which clearly established the question of compensability. Instead of presenting these cases, I wish to review briefly their patterns on the hands:

*The photographs of the cases here described will appear in my forthcoming book, Contact Dermatitis, to be published by Charles C Thomas, Springfield, Ill., 1953.

If a fingertip type lesion occurs in a draftsman due to the cedar wood of a pencil, there is no need for further investigation. There can be no question but that this is an occupational lesion.

A lesion of the finger cap type due to thimble is common in seamstresses. In butchers, we encounter the lateral palm type design from the lacquer of the meat cutter. The central palm type lesion is common in bricklayers, from the dye of bricks. This is the pattern which always indicates gripping the end of an oblong object. The dry, scaly and chronic appearance of the lesion suggests multiple contacts.

A tire salesman presented a lesion of the central palm type associated with involvement of the interdigital areas. The condition occurred at the time when he started to paint tires. Further details in this patient's history suggested sensitivity to either rubber or paint. The pattern of the lesion clearly ruled out these possibilities. A rubber tire dermatitis could not have involved the interdigital spaces. A dermatitis from paint would have produced more irritation on the first two fingers. Instead, the pattern suggested a soap dispenser lesion. It was soon demonstrated that a new detergent which the patient began to use at that time was responsible.

A grocery clerk had lesions of the finger tip type on both index fingers due to the fact that every morning at the beginning of his daily duties he turned the nickel dial of a rubber stamp. Lesions of the finger cap type from a plastic or metal thimble are so characteristic that they cannot be mistaken. The dermatitis is compensable, if the patient is a seamstress by occupation.

A nickel dermatitis on a doctor's hand was due to his habitually turning the key to his car door. This condition cleared up as soon as the cause was determined and eliminated. Several months later, the lesion recurred on the right index finger. It showed the pattern of the finger cap type, which clearly suggested an occupational basis. The doctor had been placed on obstetrical service where he had to use the telephone dial repeatedly. The lacquer of the holes of the dial had worn off, and thus he again came in habitual contact with nickel.

A hospital clerk presented a very chronic and severe dermatitis on both hands. Since this started when he took up his present job, the question of compensability came up. The lesion was characteristic of a "flat surface type." In addition, it involved an area on the knuckles. The flat surface responsible for it was easily identified as that of a rubber pad on his desk. The eruption on the knuckles occurred because the patient was an amputee and had to lean heavily on the rubber desk pad when getting up from his desk.

Another lesion combining a dermatitis on the volar part of the hand with one of dorsal parts of the fingers is very characteristic of an occupational contact, namely, polishing furniture. The areas involved are those which have friction with the object to be polished.

SUMMARY

Thus it is demonstrated that observation of the pattern of a lesion clearly indicates whether or not a dermatitis is due to occupational sources.

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THE NEUROLOGIST LOOKS AT DISCIPLINE

Fortunately, we are no longer dependent on empiric systems, such as theology, sociology, armchair philosophy, or even couch psychoanalysis, for our understanding of the processes of learning, and the establishment of the neuroses. Instructive as these systems have been, some founded on long ages of human experience, they have produced only a discordant Babel of strident voices. Witness the "to spank or not to spank" controversies, the doctrines of "self-expression," and the puerile debates over the weaning and feeding of babies, the waywardness of youth, and sex education, both in and out of schools. Leaving aside such confusing counsel, one may turn instead to a body of carefully controlled experimental evidence on the formation of habit, and the production of the neuroses in animals. Limited though these are, at present, they represent the early fruit of our first objective approach to the molding of character, and to its distortions, the neuroses. At last, a little experimental evidence is available, free of the suppositions of mysticism of centuries of superstition not yet at an end.—ROLAND P. MACKAY, M.D., J.A.M.A. 135:399-408, 1947.

ALLERGIST WANTED

Wanted: an allergist to associate with another allergist in the Pacific Coast area. Should be a young man certified or eligible for certification for internal medicine, and having a good background in allergy.

Please direct all inquiries to Assistant Managing Editor, ANNALS OF ALLERGY, 401 LaSalle Medical Building, Minneapolis 2, Minn.

TRIODE IN BRONCHIAL ASTHMA

HENRY D. OGDEN, M.D., F.A.C.A.; FRANK P. INCAPRERA, M.D.;
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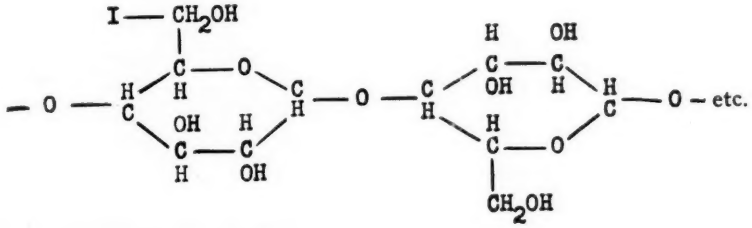
New Orleans, Louisiana

ABOUT ten years ago a research chemist, Dr. Wallace L. Minto, set about developing a substance to be used as a therapeutic source of iodine which would be superior in effectiveness to those already available, and at the same time avoid or lessen the toxic manifestations associated with both elemental iodine and the inorganic compounds of iodine. An organic iodide might fulfill these requirements; therefore Dr. Minto developed a relatively simple compound of refined pea starch and iodine (Triode). Chemically, this is a tri-iodide of beta-amylose and is a distinct preparation with unique physical and chemical properties.

Part of the structural formula is as follows:



Triode has the molecular structure of a helix. Each turn of the helix is comprised of six glucose residues. Iodine is attached to the CH_2OH group in each of the alternate residues, giving a total of three iodines for six glucose residues which make up the unit molecule of this compound.

Triode is a black powder which is readily soluble in cold water to the extent of approximately 15 per cent by weight. The powder and its aqueous solutions are stable when exposed to light, air, moderately strong mineral acids, to temperatures less than 100° Centigrade, and in a pH of 0.05 to pH of 8.5.

Hodge, Maynard, and Pfaff[2] conducted toxicity tests on animals and showed that toxic symptoms were elicited only by intraperitoneal injection.

It was not possible to administer orally a sufficient volume of five per cent Triode solution to cause acute reactions in either rats or the more sensitive rabbits, since the volumes administered by stomach tubes were, at the highest dosage used, approximately equal to the ultimate capacity of the animals' stomachs.

Rats survived oral doses of up to 800 mg of Triode per kilo of body weight.

From the Department of Medicine, Louisiana State University School of Medicine.
Acknowledgment is made of the assistance of Charles Hemelrike, Ph.D., Director of Pharmaceuticals, Thomas Jordan, Inc., New Orleans.

Assuming that human and animal toxicity are similar (a presumption which is not always valid), a normal adult of 150 pounds would be expected to tolerate 68 gm of Triode in a single dose—the equivalent of ingesting 450 tablets of 20 mg of combined iodine—without producing any toxic symptoms. The average therapeutic dose of Triode is five 20 mg tablets per day. Many patients have received seven tablets daily for many months and not a single case of toxicity has been noted. Triode can, therefore, be considered to have a very wide range of safety.

PHARMACOLOGY

The action of Triode is similar to that of other iodides. Some of the conditions for which iodides have been used are: thyroid disease, mycotic infections of the lungs, bronchial asthma and pulmonary conditions.

A. *Thyroid Disease.* A summary (Jaenike and Nasset[4]) of the relation of Triode to some thyroid functions is as follows:

1. Iodinated β-amylose, tridine,* prevents partially the thyroid hyperplasia caused by thiouracil. In this respect it acts like potassium iodide. Tridine, except in toxic concentrations, has no effect on the metabolic rate.
2. In rats receiving thyroxin, tridine, in dosages of 1, 3 and 5 per cent of the diet, has no significant effect on either the size of the organs or the metabolic rate.
3. In young rats all dosages of tridine (1, 3 and 5 per cent) are deleterious with respect to consumption of food and gain in body weight.
4. In thiouracil-treated rats, 3 per cent tridine is indistinguishable in its effects from an equivalent (0.77 per cent) amount of KI†.
5. The data from the present series of experiments on seventy-eight rats suggest that tridine when administered by mouth exerts its effect by virtue of its iodine content, and when given in equivalet amounts cannot be distinguished from KI.

B. Mycotic Infections of the Lungs.

Bieberdorf,[1] in co-operation with staff physicians at Santa Rosa and W.O.W. Hospital, administered Triode to thirty-one patients with various mycotic infections, in dosages of 320, 360 and even 450 mg of combined iodine daily, with no marked side reactions. Good therapeutic results were obtained in many cases.

C. Bronchial Asthma.

Bronchial asthma is due to one or more of the following factors: bronchial constriction, mucosal edema or mucus plugs in the tracheobronchial tree.

*The first name of Triode was Tridine, and original research was done under the latter name.

It has been recognized that iodides are very efficacious in the symptomatic management of chronic bronchial asthma. The presence of inspissated plugs of mucus are an important cause of obstruction in chronic recurrent asthma. As iodides are readily excreted through the bronchial wall, their administration has a tendency to help liquefy the thick tenacious mucus in the bronchial lumen. Hollinger, Bosch and Poncher,[3] who made direct bronchoscopic studies, showed that iodides had a better expectorant effect than ammonium chloride.

It is also recognized that iodides have been and are still widely accepted as a symptomatic treatment of bronchial asthma. They are used in the composition of many proprietary medications.

Because many patients cannot well tolerate large doses of the inorganic iodides, and since Triode has been shown to be a good source of iodine and well tolerated, it was decided to clinically evaluate the effect of Triode on a group of asthmatic patients.

The following preliminary studies were performed in the Outpatient Allergy Clinics of Louisiana State University School of Medicine, Charity Hospital, New Orleans.

METHOD OF STUDY

Thirty-one chronic asthmatic patients, ranging in age from ten to seventy years, were selected. All patients had chest x-rays, medical consultations to rule out other organic diseases, and were required to report weekly during the six months of the study. Blood pressure, pulse rate, urinalyses and total and differential blood counts were recorded during all phases of the therapy, and in no instance was there any abnormal change. The patients' comments concerning frequency, length and severity of attacks were noted.

Triode* was made available in 120.8 mg tablets, each containing 20 mg of combined iodine.

In the preliminary study herein reported, we were primarily interested in determining the patients' tolerance, and subjective evaluation of Triode as a symptomatic medication. We are currently making a second controlled study in which the efficacy of Triode is being compared with a placebo. In this new study, the placebo has the same appearance as Triode, and even those who are conducting the study are not aware which compound is being used. For months the patient is alternated between Triode and the placebo. At the end of this study it will be possible to compare the response of the individual to these two compounds, and to statistically evaluate this new organic iodide.

In the first week of this preliminary study, fifteen patients in the Negro clinic were given 40 mg of combined iodine per day. This dosage proved to be inadequate and some patients lost interest in the study. When the daily dosage was increased to 60 mg, clinical results became more definite.

During the third week, the dosage was increased to 100 mg per day.

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*Supplied by Thomas Jordan, Inc., New Orleans.

TABLE I. COUGH

Effect	Triode 26 patients	Placebo 23 patients	Potassium Iodide 21 patients
No Change	11 (42.3%)	14 (61.0%)	11 (52.5%)
Increase	15 (57.7%)	8 (34.8%)	7 (33.3%)
Decrease	0 (0%)	1 (4.4%)	3 (14.3%)

The increased coughing of these patients while on Triode is attributed to greater sputum production.

TABLE II. SPUTUM

Effect	Triode 26 patients	Placebo 23 patients	Potassium Iodide 21 patients
Increase: 1+	7 (26.9%)	5 (21.8%)	5 (23.8%)
2+	9 (34.6%)	1 (4.4%)	8 (38.1%)
3+	5 (19.2%)	0 (0%)	1 (4.8%)
4+	1 (3.9%)	1 (4.4%)	0 (0%)
Total Increase in Sputum	22 (84.6%)	7 (30.6%)	14 (66.7%)
No Increase	4 (15.4%)	16 (69.4%)	7 (33.3%)

TABLE III. ABILITY TO SLEEP

Effect	Triode 26 patients	Placebo 23 patients	Potassium Iodide 21 patients
No Increase	11 (42.3%)	10 (43.5%)	7 (33.3%)
Increase	15 (57.7%)	5 (21.8%)	11 (52.5%)
Decrease	0 (0%)	8 (34.8%)	3 (14.3%)

Assuming that the ability to sleep well depends upon the severity of asthma.

Almost all patients had increased expectoration, and often reported coughing up "long strings of mucus." Generally, they stated that there was less wheezing and that breathing was easier. Also, they were able to sleep better because their asthma was improved.

Sixteen patients in the white clinic were then started on 100 mg Triode per day, with the same results.

Then, in order to determine the tolerance, Triode was increased to 140 mg of combined iodine per day in both clinics. Practically all patients in this series were maintained on this dosage.

Although thirty-one patients were included in the original series, the results have been computed on only twenty-six patients. The remaining five apparently had spontaneous remissions or proved to be unsuitable for clinical evaluation. Effects of Triode were compared with those of placebo as well as a saturated solution of potassium iodide (10 drops tid).

Based on the patients' reported experiences, the following observations of certain symptoms (severity of cough, amount of sputum and ability to sleep) were made and are reported in Table I, II and III.

All of the observations in Tables I, II and III are based on careful reviewing of each individual case.

The general response of the patient to Triode was compared with that to placebo and potassium iodide. It was obvious that the response to Triode

exceeded the results obtained by the other two measures. As a subjective evaluation the data is summarized in Table IV.

TABLE IV. RESULTS WITH TRIODE

Excellent	2 of 26 patients	or 7.7%
Good	8 of 26 patients	or 30.8%
Fair	11 of 26 patients	or 42.3%
No benefit	5 of 26 patients	or 19.2%

As can be seen in Table IV, twenty-one of twenty-six patients with chronic asthma, or 80.8 per cent, showed benefits from Triode. As far as we know, no antispasmodic or antiallergic drugs were given with it.

SIDE REACTIONS

The chief side reactions observed were transient dizziness in eight of the twenty-six cases; polyuria in five; nervousness in three; weight loss and dry mouth in two. Five patients in the series reported one of the following reactions: sleepiness, hyperhidrosis, sore throat, hypersalivation, or nausea.

Most of these side reactions were extremely evanescent, many of them being reported on the first day only. Therefore, most of them may be discounted as being psychological reactions rather than true side reactions.

In no case did side reactions persist as therapy continued beyond three weeks on maximum dosage. The patients knew that a new drug was being evaluated and this factor must be taken into consideration. It is the conclusion of the authors that no side reactions of any consequence occurred. Also, in no case was iodism observed.

All patients were routinely scratch-tested with a sterile 5 per cent Triode solution. All tests were negative. Patch tests were also made with the same solution for forty-eight hours, and these tests were also all negative.

It is worthy of note that Triode was given to two practicing physicians (J.B.L. and A.M.P.) who had bronchial asthma and who experienced severe side reactions with inorganic iodides. They were able to take Triode over extended periods without any difficulty, and both physicians reported that this drug improved their asthmatic symptoms.

SUMMARY

1. Triode (a tri-iodide of beta-amylose) was administered to a group of asthmatic patients in the Louisiana State University School of Medicine, Outpatient Allergy Clinics, at Charity Hospital.

2. This compound was subjectively evaluated. Overall evaluation indicated that Triode was superior to a saturated solution of potassium iodide and to a placebo, and of twenty-six patients, twenty-one reported symptomatic improvement.

3. Triode increased the production of sputum, thereby lessening the degree of asthma. There was more cough and the patient slept better.

4. This organic iodide was well tolerated, and the few side reactions were of a minor nature and were evanescent.

5. No allergic manifestations to Triode and no iodism were observed in any case.

6. Two practicing physicians, intolerant of inorganic iodides, experienced no side reactions with this organic iodide, and stated that their asthma was improved.

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1706 Pere Marquette Bldg.

POSTGRADUATE COURSE IN DIABETES AND BASIC METABOLIC PROBLEMS

The first Postgraduate Course in Diabetes and Basic Metabolic Problems to be conducted by the American Diabetes Association will be offered under the direction of Charles H. Best, C.B.E., M.D., F.R.S., Director of the Banting and Best Department of Medical Research of the University of Toronto, on January 19, 20, 21, 1953, at the University of Toronto, Canada.

Developed by the Association's Committee on Postgraduate Education, under the chairmanship of Edward L. Bortz, M.D., the Course will have as its Clinical Director, Ray F. Farquharson, M.B., Professor of Medicine of the University of Toronto, and Andrew L. Chute, M.D., Professor of Pediatrics of the University of Toronto, will act as Associate Clinical Director.

Over thirty lectures and round-table discussions have been planned as well as a social evening. The Course is open to non-member physicians as well as members of the American Diabetes Association, but the number of registrants will be limited to 100. Fees are $20 to members, $40 to non-members. Details of the three-day program and registration and hotel information may be obtained from J. Richard Connelly, Executive Director, American Diabetes Association, 11 West 42nd Street, New York 36, N. Y.

CHLOR-TRIMETON MALEATE REPEAT ACTION TABLETS IN THE TREATMENT OF PRURITIC DERMATOSES

RUDOLPH S. LACKENBACHER, M.D.

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SINCE the discovery of the first antihistamine, Antergan, many other antihistaminic drugs have been developed and recommended. Among other diseases they are recommended for the relief of pruritus from various causes.

The exact mechanism of action of antihistamines still is unknown. Their therapeutic value, however, in various allergic diseases, especially nasal allergies, hay fever, asthma, urticaria, and severe drug sensitivity reactions, is well established.

With the advent of more and more antihistaminic substances, it was inevitable that they would be investigated in the treatment of itching skin diseases. They have proved especially valuable in contact dermatitis, atopic dermatitis, pruritus and dermatitis anogenitalis, and generalized pruritus, when used orally, parenterally, or locally as ointment or lotion.

The incidence of side actions caused by antihistamines varies widely. An incidence as high as 29 per cent has been reported for eight well-known antihistamines.[5] Drugs with a lower incidence of side actions, however, have become available in recent years.

By a process of trial and error, I came to use in allergic skin conditions Chlor-Trimeton, an antihistamine with a reported low incidence of side actions. In patients with pruritic dermatoses, this drug relieved itching with a complete absence of side effects.

Within the last year a new dosage form, Chlor-Trimeton Maleate Repeat Action Tablets,* became available. These tablets were said to have a longer antihistaminic effect than the approximately four-hour effect obtained with single doses of the drug. Four milligrams of Chlor-Trimeton is contained in the tablet coating for an immediate antihistaminic effect. A second 4 mg. dose is released from the enteric-coated core of the tablet in about four hours. Use of the tablets revealed that they did provide the prolonged antihistaminic effect claimed. Consequently, these 8 mg tablets were substituted for the Chlor-Trimeton tablets containing a single dose in treating patients with pruritic dermatoses.

Chlor-Trimeton is a highly active antihistaminic substance.[10] Toxicity tests in animals have shown no toxic or cumulative effects.[6] The drug has proved to be safe in clinical use.[1,8] A report on the use of the repeat action tablets noted that side actions did not occur.[11]

Report (enlarged) read at the Meeting of the Metropolitan Dermatological Society of Chicago, March 12, 1952.

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*Manufactured by Schering Corporation, Bloomfield, N. J.

STUDY

During the past year, 233 patients with pruritic skin conditions have been treated in private practice with Chlor-Trimeton Maleate Repeat Action Tablets. The patients ranged in age from twelve to seventy-eight years. The numbers of patients with the various diseases treated were as follows:

Diagnosis	*No. Patients*
Contact Dermatitis, or Contact Eczema of face and neck	48
Contact Dermatitis, or Contact Eczema of hands and feet	74
Atopic Dermatitis (Disseminated Neurodermatitis)	39
Circumscribed Neurodermatitis (Lichen simplex chronicus)	50
Dermatitis and Pruritus Anogenitalis	8
Acute and Chronic Hives	9
Miscellaneous Pruritic Dermatoses	5
Total patients	233

The patients were usually seen once a week. An attempt was made in all instances to find the causative agent and eliminate it. Some advice was given as to diet, i.e., reduction in the use of coffee, tea, alcohol, seasonings, and spices. At the first visit and once weekly thereafter each patient received an intracutaneous injection of a histamine-protein antigen complex (0.01 cc dose increased gradually to 0.1 cc) or of 10 cc (1 Gm) of strontium bromide intravenously. The choice of drug depended on the diagnosis and the patient's emotional status. Histamine azoprotein has been shown to stimulate immunity against histamine.[2,9]

For each patient, two Chlor-Trimeton Maleate Repeat Action Tablets were prescribed daily, one to be taken after breakfast and one on retiring. Some children under twelve have been treated with a combination of Chlor-Trimeton Maleate Syrup and Syrup Neocalglucon.® Besides the tablet prescription, each patient received a prescription for a mild ointment* or lotion, depending on the condition of the skin.

In general, ten to twelve hours of antihistaminic effect was obtained with each repeat action tablet so that two tablets daily were sufficient. This was distinctly advantageous in that many of the patients were employed. Had shorter-acting medication inadvertently been left at home, the effect of the single morning dose of the drug would have been insufficient to tide the patient over until he could return for a subsequent dose. Approximately 4 per cent of the patients required three tablets daily during the first weeks of their treatment in order to obtain relief from itching. These were patients with pruritus anogenitalis and disseminated neurodermatitis.

*Following are the compositions of the ointments used:
Ointment I: Burow's Solution 10, Lanolin or Aquaphor 20, Zinc Oxide Paste 30.
Ointment II: Boric Acid Solution, 3 per cent, 40, Lanolin 40, White Petrolatum to make 100.

RESULTS

The patients usually responded rapidly to the treatment described and felt better in a short time. Itching was controlled. The antipruritic effect of Chlor-Trimeton did not, of course, cure the disease, but it enabled the patients to stop scratching and so to feel more comfortable. In a short time the vicious cycle of itching, scratching, and more itching could be broken. As the pruritus subsided, management of the affected skin became less difficult. Secondary complications lessened and the course of the disease shortened.

Patients felt less irritable while on medication. They slept better than before. Patients with severe, long-standing pruritic disease sometimes give a history of tenseness and emotional disturbances. Relief of tension and relaxation are essential for them. Rest in the middle of the day, preferably at lunch time, helps to relieve tension. Many patients in the group receiving Chlor-Trimeton volunteered the information that they experienced a feeling of relaxation and relief of tension.

After years of watching for side actions caused by antihistaminic drugs, all patients were cautioned at the first visit to note such effects as drowsiness, dizziness, nausea, et cetera. After a month of treatment with the repeat action tablets with no reports of adverse effects, it seemed unnecessary to advise the usual precautions in administering antihistamines. There was a remarkable absence of side actions. The drug could be continued in every instance. Patients receiving three tablets daily had no complaints of adverse effects.

Following are case histories of twelve of the patients treated.

Case 1.—R. W., a thirty-eight-year-old man had circumscribed neurodermatitis of both legs, with exacerbation for the past three months, severe pruritus and excoriations. He was first seen July 18, 1951. Treatment prescribed was two Chlor-Trimeton Maleate Repeat Action Tablets daily, Ointment I for local application and a histamine-protein antigen complex injection weekly. By July 31, the patient had improved, his skin was much softer and no new scratch effects were present. The histamine-protein antigen complex injection was repeated and Ointment I continued with 3 per cent Liquor carbonis detergens. On August 9, his skin was soft and clean, some hyperpigmentation was still visible but pruritus was absent. The patient was dismissed with directions to continue one tablet every evening for an additional two weeks.

Case 2.—R. P., a man aged forty-one, had an acute vesiculous contact dermatitis of both ears of three days' duration with severe itching and burning. He was treated with two tablets daily, Ointment II and an injection of histamine azoprotein. The condition cleared in three days and the patient was dismissed with no itching or burning.

Case 3.—W. W., a thirty-five-year-old man, had a diagnosis of pruritus and dermatitis anogenitalis of two months' duration. He was first seen April 9, 1952. He was treated with two Chlor-Trimeton tablets daily, Ointment II, and Strontium bromide was injected. By April 15, there was less itching, the skin was softer,

anal area dry and no scratch effects. The patient was dismissed and advised to take one tablet daily for two more weeks.

Case 4.—E. P., a woman, aged twenty-six, had a disseminated neurodermatitis of many years' duration affecting the scalp, face, neck, trunk, arms, and legs. She had marked lichenification, numerous excoriations, and severe itching when first seen March 20, 1952. Treatment of two Chlor-Trimeton tablets daily, Ointment II and a histamine azoprotein injection weekly was begun. The itching was relieved and lichenification started to disappear within a week. The ointment was changed to Ointment I alone and later with 3 or 5 per cent Liquor carbonis detergens. Itching completely disappeared and the patient's skin resumed a normal appearance.

Case 5.—S. S., a twenty-one-year-old woman, had lichen pilaris and pruritus when she was first seen January 5, 1952. She was treated with two Chlor-Trimeton tablets daily, Ointment II and a histamine azoprotein injection weekly. By February 5, the itching was gone, her skin much softer and no scratch effects.

Case 6.—A. R., a woman, aged sixty-five, had contact dermatitis of the eyelids and area behind the ears of three months' duration when she was first seen April 19, 1952. Treatment of two Chlor-Trimeton tablets daily, Ointment II, and a histamine azoprotein injection weekly was begun. One week later, the patient was much improved; her eyelids were soft, no longer scaly and she had less itching. On May 3, the patient looked fine. Her eyes were normal and ear affection healed.

Case 7.—J. J., a man, aged fifty, had a disseminated neurodermatitis with severe pruritus interrupting sleep. Previous treatment by another physician, including some parenteral medication, had brought no relief of itching. He was first seen April 16, 1952. He was treated with two Chlor-Trimeton tablets daily, Ointment I, and a histamine azoprotein injection weekly. On April 24, the patient felt more relaxed than during a previous lengthy period and slept through the entire night. His skin was softer and less irritated with itching reduced. After two weeks of treatment, all itching had disappeared and the patient felt more nearly normal.

Case 8.—A., a nineteen-year-old man, with a diagnosis of penicillin urticaria of one week's duration, with severe itching, was treated with three Chlor-Trimeton tablets daily, lotion and an injection of histamine azoprotein. All lesions healed within a week.

Case 9.—J. C., a twenty-five-year-old man, had a dermatitis and pruritus anogenitalis for one year with severe itching and excoriations. He was first seen April 26, 1952. Treatment with two Chlor-Trimeton tablets daily, Ointment II, and a histamine azoprotein injection weekly was begun. On May 3, there were no more scratch effects and less itching. The patient felt relaxed. On May 10, the patient was much improved, the itching gone and his skin normal in appearance. He was advised to take one tablet every evening for two additional weeks.

Case 10.—A. R., a man, aged twenty-five, had acute oozing eczema with itching and burning; it was of four weeks' duration subsequent to painting an apartment. He was first seen January 5, 1952, and treated with two Chlor-Trimeton tablets daily, Ointment II, boric acid dressings and a histamine azoprotein injection weekly. By January 12, his skin was clearing, dry and there was less itching. Treatment was continued without dressings. On January 19, his skin was normal with no itching and the patient was dismissed.

Case 11.—M. H., a forty-seven-year-old woman, had circumscribed neurodermatitis of arms and neck with severe itching, when she was first seen April 1, 1952. Treatment with two Chlor-Trimeton tablets daily, Ointment I, and a histamine azoprotein injection weekly was begun. One week later, she had less itching. On April 15, all itching was gone. The same treatment was continued with Ointment I plus 3 per cent Liquor carbonis detergens. The patient felt more relaxed and was beginning a vacation.

Case 12.—C. C. M., a man, aged forty-seven, had acute contact dermatitis of one cheek. He was first seen March 28, 1952. He was treated with two Chlor-Trimeton tablets, Ointment I, and a histamine azoprotein injection weekly. On April 4, there was less redness, less itching and the scaliness was gone. The treatment was continued. By April 11, his skin was normal with no itching and he was dismissed.

COMMENT

Experience over a year with Chlor-Trimeton Maleate Repeat Action Tablets has led to the opinion that they provide efficient antihistaminic action and are of great value in the treatment and relief of itching in pruritic dermatoses. The prolonged effect of the tablets makes them more helpful than other similar drugs in combating the most annoying symptoms of pruritic skin conditions. They often give a pleasant sense of relaxation.

SUMMARY

Two hundred thirty-three patients with pruritic skin diseases were treated with Chlor-Trimeton Maleate Repeat Action Tablets orally. The tablets are believed to be the most satisfactory antihistaminic preparation for treatment of such conditions. Itching was promptly relieved. There were no side effects from the drug. The antihistamine tablets were used in combination with injections of a histamine-protein antigen complex and local therapy with ointment or lotion.

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THE MANAGEMENT OF THE ALLERGIC CHILD

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THE allergic child is a "well" child who has a medical problem which he may have to face throughout his life. He must learn to live with his disability as must the diabetic child. Allergic disorder, however, may be more annoying and upsetting than diabetes mellitus. Because it is usually neither serious nor fatal, its possible grave effects on the child's mental and emotional development must not be underestimated. It is unfortunate that much of the current literature concerning pediatric allergy does not mention the emotional problems which are involved nor does it consider the potential serious effects of treatment regimes on the child's developing personality. Furthermore, it is apparent to anyone who has had contact with asthmatic children that emotional upheavals can precipitate an attack. An appropriate concern, therefore, for the healthy development of the child's personality is a necessary component of effective therapy.

The allergic state and the treatment regime it necessitates can warp the child's personality in many ways. Typically, the child suffers from eczema during much of his infancy. He is tortured and made sleepless by itching and sometimes painful skin. He is often tied to his crib with his every movement frustrated: he cannot even suck his thumb, the last solace of a lonely baby! Covered with weeping sores and greasy ointments, he does not receive the fondling and loving which he needs. His diet is frequently unattractive and monotonous and deprives him of the oral gratifications which a growing personality must have. In addition, he may receive painful injections at regular intervals which can condition him to mistrust and dislike other human beings. Finally, his parents may reject him because he is "abnormal." American culture demands standardization, and parents may resent this unstandardized product they have created, possibly projecting their guilt feelings onto the child, especially if his allergic state is inherited. Or they may reject him because of the trouble and expense he entails. Equally unfortunate for the child, his parents may develop an unhealthy protective attachment to him which is almost as harmful to his personality development as rejection. They may become convinced that he is ill and must be overprotected; they may not allow him to mature as a normal human being. And in an era when knowledge of infant nutrition

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is in an unhappy psychologic state of exploitation and pseudoscientific compulsion, they may develop numerous phobias about diet in general.

For the allergic child, then, there are several unhealthy psychologic factors which may be present in infancy. Physically miserable and sleepless, tied down, frustrated and hurt, he finds little joy in eating—and this joy should be one of his major satisfactions and means of becoming positively conditioned to his surrounding world. He does not receive the loving and fondling which he must have if he is to mature emotionally. Finally, his parents stunt his personality with overattachment, or, losing their capacity to love him for what he is, they reject him.

As the allergic child grows older he may develop hay fever with its recurrent periods of misery. Repeated visits to the physician for painful injections and the hazard of developing hypochondriasis, plus the possible requirement of such things as a "special" place for summer vacations, all convince the child that he differs from normal, healthy human beings.

Worst of all, the child may develop asthma. The first attack often occurs about the time when his parents think they are rid of the eczema (and allergy) problem. One or both of them may be asthmatics, and they may have conditioned their child to think of asthma as a horrible fate. Parents can bear with the acute illnesses of their children, but the recurrent annoyance and expense of asthma too easily become intolerable. Its dreaded appearance in their offspring may mean his final and complete rejection. He senses this rejection because of a condition which he cannot help, and he may then project all of his guilt feelings onto his asthma, with the result that it becomes worse. Or his parents may develop an overpowering overprotection of him, allowing him no chance to achieve maturity and keeping him a dependent, insecure child who is regularly subject to terrifying, suffocating attacks. In his school life, at a time when he might gain security from his group, he is set apart; he misses school, lags behind and fails; he acquires a defeatist inferiority complex. Soon he begins to use his asthma as an excuse for failing and for not trying. Prescribed regimes often make matters worse. The dust-free room, so glibly recommended, is difficult to make and tries his parents' tempers; it is unattractive, and his favorite possessions are thrown out—insuring further insecurity for him. His household pet may be banished. This may be his dog, which can mean a great deal to even a normal boy but which may be a fundamental emotional need to an allergic child.

The allergic child, by this time, may be badly warped. Frustrated, rejected, immature, insecure at home and with his colleagues, hypochondriacal, withdrawn, resentful and frightened, he is growing to be a neurotic adult—and his asthma becomes worse.

The serious effects of the allergic state and its treatment have been exaggerated here to show their possibilities for warping the child's personality and to make a plea that the "whole child" be considered when

his allergy is treated. Unhappily, the child with an especially severe allergy may receive therapy which is concentrated entirely on his disease, and yet it is just such a child who suffers the worst emotional trauma. This is not a plea to abandon treatment regimes but to consider the child and his parents when they are prescribed. The banishment of the family dog, for instance, may be more harmful to the child—and to his allergy—t .n was the dog itself. This is not an idle plea. These upset children are seen time and again in pediatric practice. The allergist may not always see this side of the picture. Many psychiatrists agree, furthermore, that the adult asthmatic is frequently an unhappy, neurotic person, the end result of his childhood conditioning. A good pediatric allergist must consider the whole child and the effects of the allergic state and its treatment on this child's mental and emotional development.

The allergic child presents a common problem. He represents over 5 per cent of pediatric hospital admissions, he populates one of the largest pediatric out-patient clinics, and he is ubiquitous in private practice. He and his parents must be taught to accept his disease and to live with it; he must be helped to mature emotionally. His problem does not differ greatly from that of the diabetic or the epileptic child.

The physician must learn a few general principles of healthy emotional development and keep them in mind when he works with an allergic child. He must not, however, "talk" psychiatry with parents, for often they have already read too much of this in newspapers and books.

Working first with the parents, the physician must help them to accept their child's allergic state. They must know that "every little movement has a meaning all its own." The way they smile or frown, the tensions in their voices, their attitudes toward the child's allergy, their attitudes toward their *own* allergies—these mean more to the child than volumes of words. If the parents can learn to accept the problem, they will not usually reject their child. The physician must help the parents to avoid overprotecting their child. Acceptance of the problem is helpful here also. Any idea that the child is a subnormal invalid should be disabused. Fortunately, emotional development is usually orderly and is manifested by growing independence. The child's urge to maturity and emancipation is innate, and he should be allowed to follow it.

The physician must also help the child to accept his allergic problem. The child will usually accomplish this if his parents can learn to accept it—and theirs. Most important, the physician must help the child to satisfy five fundamental psychologic needs and must bear constantly in mind how the allergic state and its treatment may interfere with this fulfillment.

The child must have a *sense of belonging,* because of *who he is,* allergic or not. For security he needs constant real affection. He is not easily fooled by the doting parent who professes to love him yet who actually loves merely what she hopes he may accomplish and the perfection she

can find through him. He senses that this is not real love, and he does not feel that he belongs and is wanted, whatever his defects or troubles. Without a sense of belonging, a child cannot achieve security and normal emotional development.

The child must achieve a *certain degree of extroversion* and must be able to find satisfaction in concrete interests in the world about him. This world must not become so drab and unsatisfying, because of soy bean meals or dust-free rooms or a banished dog, that he withdraws from it and reverts to daydreaming behind the rationalized protection of the allergic state.

The child must learn *adjustment within the group.* Modern thought stresses the individual, but there remains a need to *follow* in a group and to *belong* to a group. The Army has learned the strength and security that come to a soldier when he feels he has become part of his outfit. But the child has also a need to *lead,* and he should be allowed a few activities in which he can excel and feel that he is, indeed, an individual. The child should be guided and helped so that his allergic state does not keep him out of his group.

The child must have *experience in self-sufficiency.* He must like his group but he must be able to stand alone. His allergic state must not interfere with his innate progress toward maturity and independence.

Finally, the child must have the *experience of being needed.* Every child should be given some real responsibility, commensurate with his abilities. This is especially important for the allergic child, who must never be made to feel that he is a useless burden.

SUMMARY

The allergic child is a "well" child with a life-long problem. He must learn to live with it and must be allowed to mature emotionally in a normal manner. The physician should bear always in mind that the allergic state and its treatment regimes, constantly, but not inevitably, imperil the child's emotional development. Wise handling of the problem is difficult and the good pediatric allergist will keep the child's psychologic needs in mind. He will not forget the "whole" child while treating his allergies. And remembering the possible effects of these allergies and their treatment regimes on the child's personality, he will weigh the ultimate advantage of each prescription against its possible damage to his patient's mental health.

125 DeSota Street

Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

PITFALLS OF CLINICAL EVALUATION

If a paper on the clinical evaluation of a new drug is to be trusted, certain of the criteria of its author must be immediately apparent. Does he give us the data, or at least the references, to animal studies, done in sufficient numbers and on more than one species, especially in reference to acute and chronic toxicity? What does he tell us of the rates of absorption and methods of excretion of the drug, and of its mode of action, when known? What of the general and specific effects, and those due to cumulative doses? Are the side effects of drowsiness with an antihistaminic agent of more importance than the pharmacological effects in patients taking the medicine at any one time?

Of paramount importance is the fact that the patients treated must suffer from a single clinical entity, unless the author purposely wishes to evaluate the drug in all forms of coryza or all types of wheezing. Otherwise, the selection of patients must be rigid, those known to be cooperative and reliable being preferred above others. If possible, the selection should be made with patients of comparable age and sex, whose illness is of the same order of magnitude. Those disorders in which there is a preponderance of psychogenic factors, and those patients in whom psychological traits are most marked, should be avoided.

Whenever possible, the criteria should include objective, rather than subjective, changes—those observed in the nose, by a more apparent airway; in the chest, by increased vital capacity or diminished expiration time; in the skin, by photographs. Whenever possible, comparisons should be made with control material treated with another well established agent, or with a patient suffering from the same disorder, not undergoing the same treatment.

Controls with placebo medication are a thorny subject of debate. When used, they must imitate the drug in physical form, odor and color, and neither the physician nor the patient should know which is which. When the placebo is used to interrupt therapy, the true drug frequently may show carry-over effects. When the placebo is used to initiate therapy, the lack of effect may carry over for the initial period of observation with the use of the actual drug. In ideal clinical evaluation of the placebo, effects would be low, and the medical effects well over the "inevitable 72.5 per cent."

Interpretation of data often requires the utmost objectivity. Statistical

treatment must be valid, and of such a nature that other investigators can quickly discover what the drug is, what it does, to whom it should be given, what side effects may be expected, and what therapeutic results will follow its administration. Under these circumstances, clinical corroboration of the original results is quickly added to the literature, and the drug takes its established place in the physicians' armamentarium.

THE BASIC PROBLEM OF ALLERGY

In the past decade many remedies were suggested for the conquest of allergy. Among them were histaminase, hapamine, antihistaminics, ACTH, cortisone, many other less important drugs and substances, and finally the psychiatric approach to the treatment of allergy. Needless to say, all these various approaches to the treatment of allergy have helped to allay certain symptoms and have therefore important therapeutic value. However, they have not helped to resolve the basic vexing problem of allergy.

Were we to accept the histamine concept of the allergic phenomenon, the newer endocrine concept inherent in the use of ACTH and cortisone, or the dominant rôle of the psyche, in our present state of knowledge, as the modus operandi of the allergic reaction and put aside the antigen-antibody mechanism, I believe there would be little hope for more than mere symptomatic relief of the allergies.

The contributions based solely on the antigen-antibody concept have given us a profound insight into the fundamental nature of allergy. The most momentous of these are the following: Blackley, in 1873, discovered the specific relation that exists between pollen and hay fever and proved it by skin tests on himself. Richet's discovery of anaphylaxis, the equally important studies of Arthus on local anaphylaxis, and the description of serum sickness by von Pirquet and Schick were made at the turn of the twentieth century. The nature of the allergic antibody in man was discovered by Prausnitz and Küstner in 1921.

These studies have all given rise to the fundamental work that has been done by allergists in the specific diagnosis of allergy by means of the protein skin tests.

It is the study of the many ways and means by which antigens invade the body and produce interactions with tissue fixed antibodies that offers the greatest hope for good and lasting results. The therapy of allergy must be viewed from a constitutional and preventive standpoint. It entails a search for all offending substances, their elimination or reduction, and a definite program for building up an immunologic tolerance for the offending allergens.

The control of environmental excesses, highly antigenic food excesses, promiscuous and thoughtless use of sera and drugs, as well as the management of diseases which tend to increase the permeability and dysfunc-

tion of our protecting membranes, all tend to reduce the incidence of allergy.

For the present, there is no single drug or procedure which can do more than allay certain minor phases of the allergic symptomatology, except that directed to the offending allergen. Once the mechanism of a disease is understood, reduction of incidence may eventually follow. Recognition and understanding of the antigen antibody mechanism of the allergic state stands in the forefront of the advances of modern medicine.

In Memoriam

EDWIN F. DEPPE, M.D., F.A.C.A. (Assoc.)

We announce with deep regret the death of Dr. Edwin F. Deppe of Seattle, Washington, an Associate Fellow of the College, on Saturday, November 8, 1952.

Dr. Deppe was forty-nine years old at the time of his death. He had been in ill health for the past two years and had been conducting his practice on a part-time basis since June, 1952.

He is survived by his father, C. A. Deppe; his brother, Fritz Deppe, M.D.; and a sister, Florence Deppe, who all reside in Indiana.

Dr. Deppe was born June 10, 1905, at Sedalia, Missouri, graduated from the Franklin High School, Franklin, Indiana, and from Franklin College of the same city with a degree of A.B. in 1927. He graduated from the New York Medical College in 1931 and took his internship in Miami Valley Hospital, Dayton, Ohio. He practiced five years in Internal Medicine with the late Dr. C. D. Fife, F.A.C.P., Dayton, Ohio, and took his training in Allergy under Dr. Schonwald until the time of the latter's death. He held a professorship in Allergy at University of Washington Medical School and King County Hospitals. He was a member of the American Medical Association, King County Medical Society, Washington, and Washington State Medical Society, and a member of the King County Hospital Staff, Washington. He made a three-year study of the significant allergenic airborne nonpathogenic bacteria, their incidence, types of allergies and treatment in association with Dr. Schonwald, which was published in the ANNALS OF ALLERGY. He also made a Northwest pollen survey which was published in *Northwest Medicine* in 1948. He was one of the pioneers who reported penicillium in the treatment of intrinsic allergies.

Members of the College extend their sincere sympathy to the surviving members of the family.

Progress in Allergy

PROGRESS IN DERMATOLOGIC ALLERGY

Critique and Review of the Literature of 1951-1952

RUDOLF L. BAER, M.D., F.A.C.A. AND MORRIS LEIDER, M.D., F.A.C.A.
New York, N. Y.

With these progress notes the present writers, after reviewing the literature on dermatologic allergy for several years, relinquish the task to others. It is hoped that this change in authorship will furnish readers of these reviews with a fresh point of view in evaluating work on the fascinating and important subject of dermatologic allergy.

In turning out this "final" review and in accordance with our previous custom, we are not routinely abstracting and reporting on every article that has appeared in the literature since our last review. Rather we have been selective and have chosen a limited number of papers to describe and write about which at the same time permit us to reiterate, amplify and present our own position on many timely problems and theories of dermatologic allergy.

ALLERGIC ECZEMATOUS CONTACT DERMATITIS

Of all the various types of allergic transformation and response, allergic eczematous contact dermatitis is in some ways easiest to understand and, perhaps because of the tremendous quantity of available data, in other ways most perplexing. The characteristic allergic phenomena, i.e., the specific and acquired nature of the alteration in the capacity to react, can frequently be observed in its inception clinically; it can be demonstrated experimentally with potent allergens like the nitrochlorbenzenes; and it can be tested for with a high degree of accurate yield of positive reaction. It appears likely that all persons are capable of developing the eczematous allergic states—they are not dependent on an atopic habitus and require no special constitutional or genetic predisposition for their development. Some work of Chase[9] indicates that in guinea pigs, strains can be bred which have a greater than average capacity for the development of contact-type allergic sensitization. But there are no experimental or statistical studies which support the existence of such a familial tendency in human beings. Among the many facts that are obscure in allergic eczematous contact dermatitis are (a) the nature of the allergen (must the simple chemical always be protein-conjugated?), (b) the route of dissemination of the allergen, and (c) the question of antibodies (are there antibodies and, if so, where are they produced, how are they transported to the skin, how are they lodged there, how long do they persist in the skin; and how long does antibody-production persist once eogenous exposure to the allergen ceases?)

Year after year papers appear that concern themselves with these aspects of allergic eczematous dermatitis and slowly a more complete understanding is building up.

Perhaps one of the most significant advances in dermatologic allergy in the past few years has been conclusive proof of cross or group sensitizations. While the possibility was long known, though little appreciated, it is only with the development of chemotherapeutic and antibiotic agents

in profusion that the phenomenon became frequent enough to be clinically guessed often and experimentally proved at times. By now we know of many different chemical entities that are immunologically related because they possess molecular fractions that are similar in composition and/or in spatial arrangement.

One group, that is most interesting, very commonly encountered, and easy to work with, consists of those compounds with a primary amine in the para position on the benzene ring. Many patients that are sensitized to p-phenylenediamine, p-aminobenzoate, or a sulfonamide of proper structure and composition are then found to exhibit reactions to many other compounds of the class. The value of this realization in the definitive management of cases of contact dermatitis which seem to go on interminably is obvious. Occult contact with immunologically related compounds can, in some patients, be shown to be the cause of the chronicity.

For some time it has been clearly realized that not only contact but *ingestion* or *parenteral exhibition* of drugs or other compounds of this type may be provocative of eczematous eruptions in patients previously sensitized, or such entry induces sensitization which may then just as readily be elicited by contact with the specific drug or its immunologic relatives. As a matter of fact this very point was the reason for coining the name "allergic eczematous *contact-type* dermatitis"[67] which recognizes that in principle there is no difference between an eczematous allergic reaction which has been engendered or elicited by contact, ingestion, inhalation or injection. A study presented by Sidi and Dobkevitch-Morrill[63] confirms all of the above points with experiments in which the related allergens were administered by injection and ingestion.

In two patients with allergic sensitivity to vioform and in one sensitive to diodoquin, Leifer and Steiner[40] studied the chemical grouping involved in the allergic reaction. It was noted that there was group sensitivity to the halogenated hydroxyquinolines. Neither non-halogenated hydroxyquinolines nor halogens alone were capable of eliciting the reaction. However, in all three subjects reactions were elicited with carboxylated pyridines and the authors consider the possibility that these are breakdown products, with the actual antigenic complex forming from the halogenated hydroxyquinolines.

Although cross-sensitization and cross-reactivity is by now a well established and more readily recognized phenomenon, it is still a cause for wonder why all compounds of a homologously related class do not show the cross-reactivity. In some instances nearly identical substances, differing only in factors like dextro- or levo-rotary power, or some other seemingly "trivial" difference as far as immunology goes, do not cross-sensitize and cross-react. The experiments of Eisen, Orris and Belman[17] seem to show that ability to combine irreversibly with protein is a factor in determining which substances will act as elicitors in animals and men who have become sensitized by a chemically different, yet related, compound. This confirms for the elicitors what was shown to be true for the sensitizers many years ago (1935) by Landsteiner and Jacobs[36] who demonstrated in animals that the sensitizing capacity of nitro- and chlor-substituted benzenes paralleled the lability of their Cl and NO_2 groups. This in turn indicated that it is the capacity of these substances to combine with proteins which is a major factor in determining their high sensitizing capacity. Subsequently in 1938 Sulzberger and Baer[68] were able to show that the same principles appear to apply in sensitizations in human beings.

Peck[45] reviews some earlier examples of cross-sensitization events and then goes on to reëmphasize the problem with regard to the antihistamines. Four cases are cited of cross-sensitization to several antihistamines following an original sensitization to one of them. This is understandable from structural and other immunologic similarity of many of the antihistamines. But then it is claimed that cross-sensitization was noted to chemical entities that have no apparent similarity, for example, thephorin and paraphenylenediamine. Peck considers the possibility that paraphenylenediamine and thephorin in their metabolism attain points of chemical and immunologic similarity. This may be true, but for these compounds we know of no reasonable chemical explanation for such a cross-sensitization. On the other hand, the cases in which this occurred may be simple coincidences of two sensitizations in a sequence which only appeared as cross-sensitization because they were observed simultaneously. No matter how tempting it may be, we do not believe that it is wise to speak of cross-sensitization between two compounds where there is no evidence of a chemical relationship even during metabolism.

Attempts at hyposensitization with *Rhus toxicodendron* extracts should not be made without due consideration for the dangers involved. We have previously stated our opposition to the indiscriminate use of the usually unstandardized rhus antigens. An uncommon complication is reported by Shaffer, Burgoon and Gosman[60] in two cases where acute glomerulonephritis developed. In one of these cases there was recovery. In the other, a man aged sixty-four who had received rhus antigen injections for an acute dermatitis, death ensued (apparently forty days after four daily injections). The following are among the many other facts which militate against the unfortunately still widely practiced "specific treatment" of acute poison ivy dermatitis as stated by Sulzberger and Baer:[69] (a) there is a complete lack of scientifically admissible evidence that specific extracts have a beneficial effect on the course of acute poison ivy dermatitis, (b) on the contrary there is much evidence that the skin lesions are not infrequently made worse by the specific extracts, and (c) the commercially available extracts are as a rule not even crudely standardized on a biologic basis—even though the possibility exists of fairly accurate standardization, using certain dilutions of 3-pentadecylcatechol or related compounds as a standard.

Another uncontrolled series of cases in which successful peroral prophylaxis of poison ivy dermatitis is said to have occurred is reported by Besser and Urbach.[7] While we do not doubt that specific oral hyposensitization is clinically successful in some cases, the evidence presented in this paper seems inadequate to us to substantiate such a claim.

First reports have appeared on the effects of topical application or intracutaneous injection of compound F (17-hydroxycorticosterone-21-acetate). Goldman, Preston and Rockwell[24] injected this substance intracutaneously and, after an unspecified interval, carried out patch tests over the injected sites with eczematogenic allergens and primary irritants. The number of tests and subjects involved is too small to permit definite conclusions. Their results to date show a frequent complete or marked inhibition of the allergic eczematous response but no inhibition of the response to the irritant effects of turpentine and cantharidin in two patients tested. The investigators remark that the zone of inhibition exhibited by their patients was not limited to the immediate area of injection of compound F. Definite local inhibition of the tuberculin and tuberculin-type response is also mentioned.

Nilzen[44] reports that such interference with local tissue reactivity in *animals* sensitive to dinitrochlorbenzene was not produced by compound E (cortisone) injected intracutaneously or applied by inunction, nor was there a decrease in the skin reaction to croton oil. However, systemically administered cortisone decreased skin reactivity to some, though not all, primary irritants tested as well as allergic skin reactivity to 2, 4 dinitrochlorbenzene. Neither systemic nor local treatment with cortisone prevented sensitization to 2, 4 dinitrochlorbenzene.

Severe acute allergic eczematous contact dermatitis yields in a really remarkable fashion to the administration of cortisone and ACTH. Among the reports dealing with this form of therapy are those of Falk, Allende and Bennett[21] and Gay and Murgatroyd.[22] We, as many others, by now have had an extensive experience with the use of cortisone in contact dermatitis and our opinion on its use can be summarized as follows:

(a) The administration of cortisone is the single most effective measure for the control of severe acute contact dermatitis that has yet come to our attention.

(b) Cortisone is *not* indicated in mild cases unless there are *unusual circumstances* which make it absolutely essential that the patient be as free as possible of dermatitis within twenty-four to forty-eight hours.

(c) Cortisone therapy is entirely palliative and must be combined with complete avoidance or elimination of the allergen or, if the allergen is not known, with a most diligent search for the cause in each case.

(d) Cortisone will clear the eruption and still will not interfere with the elicitation of patch test reactions. This makes cortisone therapy actually an adjunct in the etiologic investigation of cases of allergic contact dermatitis.

(e) Severe acute allergic contact dermatitis is perhaps a more "ideal" indication for cortisone therapy than any other of the commoner diseases because it is a self-limited disease which often runs its course to termination in a few days to weeks, and thus will not recur when the drug is gradually withdrawn after a few days to a few weeks, provided there is no renewed exposure to the causal agent.

(f) The patient must not have any of the diseases which form a contraindication to cortisone therapy and all the usual precautions must be strictly observed.

Among all the other mysteries of the pathogenesis of allergic eczema, two that have exercised research workers in recent years are (a) proof of mediation of the reaction of allergic eczema by antibodies and (b) the source of production of antibodies. Haxthausen,[29,30] who has been one of the foremost workers in this field, recounts his experiences with passive transfer of allergic eczema by transplantation experiments. Despite all the difficulties of working with homotransplants in human beings—difficulties of securing donors and recipients, and difficulties of securing good takes of sufficient duration to permit the performance of readable patch tests—despite all this, Haxthausen shows convincingly that the mediators of the eczematous allergic reaction do not arise in the skin and are not demonstrable there for long, but are brought to it from below or from the circulation. In about a score of such experiments out of which fourteen were technically successful enough to permit completion of patch testing, eleven showed acquisition of specific sensitivity by a non-sensitive transplant when it was grafted onto a sensitive recipient. In previous experiments Haxthausen also had shown loss of sensitivity of a trans-

plant from a sensitive donor when it was grafted onto an insensitive recipient. The conclusion from these experiments is that the skin itself apparently does not produce that "something" (antibodies) that makes the skin capable of reacting in allergic eczema but that that "something" comes to it from elsewhere.

All the evidence accumulated in *animal* experiments by Landsteiner and Chase and others indicates that the lymphocytes and monocytes are the carriers of the presumptive antibodies in the contact-type of allergic sensitivity. This suggested that one might be able to achieve either local or general passive transfer of allergic eczematous contact-type sensitivity in *human beings* through the transfer of white blood cells from sensitive donors to non-sensitive recipients.

Subsequent to tests done in 1947 by Haxthausen, three recent series of experiments dealing with attempts at *passive* transfer by means of white cell suspensions have been reported. In one series Baer and Sulzberger[4] used the technique of H. J. Lawrence[37] and in a second series Baer, Serri and Kirman[3] employed a technique which reduced to one hour the time necessary for the separation of viable white cells from the donor's blood and their injection into the non-sensitive recipient's skin. A still different technique was used by Haxthausen.[31]

The investigators involved in all three series, which add up to many separate trials of passive transfer, agree that they failed to find any definite evidence that allergic eczematous contact-type sensitivity can be passively transferred from one human being to another. However, some of the recipients developed what appeared to be an *active* sensitization to the allergen with which they were tested. Baer and his collaborators report an overall incidence of 11 per cent of what they believe are probably active sensitizations. They speculate that the white cells of human beings with allergic eczematous sensitization may contain a factor which, when injected into non-sensitive recipients, will increase the recipient's susceptibility to active allergic eczematous sensitization to the allergen to which the cell donor is sensitive. They cite work of Chase[10] and of Harris and Harris[27] which speaks in favor of such a possibility in animals with respect to the formation of precipitins, anaphylactic antibodies and other types of antibodies.

The question as to how the presumptive antibodies carried by the lymphocytes and monocytes reach the epidermis is also being brought closer to solution. The work of Andrew and Andrew,[1] Herman Pinkus[48] and Hagerman[26] has shown that lymphocytes are found in the epidermis with regularity. One may assume that these lymphocytes deliver their antibody content to the epidermal cells, thus explaining the regular replenishment of antibodies in the skin. However, the theory of Andrew and Andrew that such lymphocytes become part of the epidermal structure and start multiplying there is entirely unproven, and extremely unlikely from the phylogenetic viewpoint.

There are innumerable questions which are unanswered in this most important field. Why do some skin areas stay permanently more sensitive than other skin areas? Do more lymphocytes reach such areas? Have such areas a greater attraction for lymphocytes or a greater storing capacity for the antibodies than other areas? How does one explain cases of sensitivity limited to one skin area and cases where just one skin area stays insensitive?

Further interesting work which indicates the role which the lymphocytes and monocytes play in the eczematous allergic reaction was done by Nex-

mand.[43] He showed that the cellular content of the blister fluid from allergic eczematous patch test reactions is predominantly mononuclear (lymphocytes and monocytes) as opposed to that of primary irritant reactions which is predominantly polymorphonuclear. These studies were confirmed by Baer and Yanowitz[5] who demonstrated that the cells in the blister fluid of clinical lesions of allergic eczema also are predominantly mononuclear. Nexmand furthermore stated that the cells in the inflammatory perivascular infiltrate in allergic eczema tend to be predominantly mononuclear.

Curtis[14] also attempted to demonstrate antibodies in allergic eczematous contact dermatitis. He used the passive transfer method with blister fluid and with skin protein extracts, prepared by ultrasonic radiation and homogenization. The results were negative in all of five experimental cases.

A most timely and interesting approach to the problem of allergic eczematous sensitivity has been taken by Everett, Livingood, Pomerat and Hu.[19] They made explants of human skin obtained from sensitive and non-sensitive subjects, on tissue culture media and then sought to ascertain the minimal inhibitory dose and least injurious dose to the explants of such allergens as rhus oleoresin, 2, 4 dinitrochlorbenzene and old tuberculin. In tissue cultures no difference was observed in the amount of outgrowth of skin from sensitive and non-sensitive persons when the allergens were introduced into the culture medium. Thus there was no evidence of increased sensitivity in the explants from patients with allergic eczematous sensitivity. These results could be due to technical factors or due to the absence of the presumptive antibodies in the explants.

Seeborg's[58] studies of the induction of eczematous sensitivity when eczematogenous allergens are introduced by various routes, are of interest to ascertain which routes can be successfully used and as to the site of antibody formation. Sensitization by epicutaneous contact of eczematogenous allergens is the usual clinical event. Intracutaneous placement has been shown to be an efficient artificial means of sensitizing, whereas subcutaneous deposition is not a good method. Seeborg performed comparative experiments in guinea pigs with dinitrochlorbenzene utilizing epicutaneous, intracutaneous, subcutaneous and lymph gland depots. He found that deposition of the allergen in the lymph gland is equally good in inducing sensitization as epicutaneous deposition.

A number of papers have appeared during the past year which either describe new eczematogenic allergens or bring new information regarding previously known allergens.

Sulzberger and Lazar[71] remark that lanolin sensitivity is uncommon but, when it is incurred, it is a serious problem in management because of the ubiquitous distribution of wool fat in multitudinous materials used in modern living. They attempted to ascertain which fractions in the complex of lanolin are responsible for the allergenic action of this material and found it to be in the mixed alcohols of wool fat. However, the precise ingredient or ingredients could not be further identified because they are as yet not chemically resolved. They speculate that wool fat may contain substances in common with human sebum and in that case one might investigate sensitization to body-own or autochthonous materials as a possible cause of certain etiologically unresolved dermatoses like seborrheic dermatitis and even systemic conditions like the xanthomatoses.

Leider, Furman and Fisher[39] show that rubber is now assuming a position among the more common causes of allergic eczematous contact dermatitis. Like nail polish, rubber does not have a high index of sensitizing

potential, but from the frequency and continuity of rubber contact, the prevalence rate, i.e., the number of cases of sensitization existing at any time, is becoming huge. In the compilation cited, rubber makeup sponges, gloves, condoms rubber in garments and a host of miscellaneous other rubber household, industrial and clothing articles were found to be causes in particular patients.

Rostenberg and Perkins[54] report a case of simultaneous sensitization to nickel, cobalt and gold. The sensitization to gold is thought to be independent of the other two. However, they state that there is frequently cross-sensitization to nickel and cobalt. They show a lymphangitic streak after an intracutaneous test with cobalt solution which is attributed to allergen dissipation via the lymphatics, an event which had been described also by Haxthausen.[28]

Chromic salts have long been known to be causes of primary irritant dermatitis on human skin. Sensitizations to chromium in concentrations of its salts that are not primarily irritant have also been observed, but their full importance is only now being completely realized. Winston and Walsh[78] report a case in a machinist, working in a Diesel locomotive shop, who developed a dermatitis that was traced by patch test to the small concentrations of sodium bichromate contained as an anti-oxidant in radiator fluid of locomotives. An even greater source of contact with chrome salts has recently been discovered in the processing and use of cement. Jaeger and Pelloni[33] discovered that 94 per cent of workers with cement dermatitis reacted to an 0.5 per cent potassium bichromate solution as compared with 5 per cent who had eczema due to other causes. Thus it appears that the well-known cement workers' eczema is usually due to the chromate content of the cement rather than other factors.

Considering the antiquity and volume of wood gathering and woodworking activity, it is surprising, and fortunate, that sensitization to active principles in wood does not occur often. Occasional and sporadic cases are seen of sensitization to pine, fir, maple, oak, et cetera, but the commonest wood we know that causes sensitization is probably cocobolo wood. DeJong, Lenstra and Vermeer[16] report five cases of sensitization to another wood (Peroba da Campos) from which they were able to isolate a crystalline substance and prove it to be the sensitizing substance. It is notable that this wood like cocobolo is of central South American (Brazilian) habitat. There may be a difference in the content and quality of allergenic principles between tropical and temperate zone lumbers.

Lamb and Lain[35] present three cases of allergic eczematous contact dermatitis traced to azo dyes used to color gasoline. That azo dyes can sensitize and cross-sensitize is again well established. But the realization that eruptions caused by "gasoline" may be caused by an added constituent rather than the hydrocarbon is valuable and instructive.

Sarcoid reactions produced by beryllium compounds are well known. Some beryllium salts are also caustic and produce ulcers. Curtis[13] now brings to attention the allergenic sensitizing capacity of beryllium salts. It seems that like other metals, e.g., mercury, nickel, chromium, some beryllium compounds are capable of inducing allergic eczematous sensitization. With the increasing use of this metal in industry the problem of occupational dermatitis from it is bound to grow. We venture to predict that other rare metals and trace substances will be found to become causes of occupational dermatitis as their importance in modern industrial processes becomes greater and their use more extensive. We dread to think what will happen when such new elements as delirium and pandemonium come into general circulation.

Peck and co-workers in a previous paper[47] studied reactions to adhesive tape and found that the reactions could be divided into three kinds, namely (a) an immediate and fleeting erythema that results from the trauma of removal of the tape, (b) a reaction of sensitization, and (c) a reaction of irritation. In a recent paper[46] the problems are further explored and previous conclusions confirmed by greater detail of clinical, bacteriologic and histopathologic study.

In examining the findings, we would interpret the first reaction as being at least in part inevitable "red" dermographism resulting from the trauma of removal of tape. It probably occurs in everyone because the trauma is severe enough to produce erythema, and in persons with urticarial dermographism we have seen whealing occur. The reaction of "irritation" is correctly attributed to mechanical obstruction of sweat gland ostia and promotion of bacterial infection. This too must be a nearly inevitable consequence of too long application of tape. If this is spoken of as a reaction of irritation we think that it would be preferable to speak of "nonspecific irritation." Otherwise it seems to us a better descriptive designation would be the reaction of dyshidrosis and infection. Finally, the reaction of true allergic sensitivity is noted but remarked to be rare.

ATOPIC DERMATITIS

Atopic dermatitis continues to be as exasperating an etiologic and clinical problem as ever. And because it is so unresolved the confusion regarding diagnosis and treatment that surround it is great. As a differential diagnostic problem it sometimes needs differentiation from seborrheic dermatitis, contact dermatitis, lichen chronicus simplex and other eczematoid conditions. There is a clear connection with certain features which are characteristic of the atopic form of allergy in some but by no means in all cases, as can be demonstrated by multiple immediate wheal reactions to common protein allergens and by association with such classical atopic conditions as allergic rhinitis and asthma. Despite this, allergic investigations and treatment stemming from such investigations are *not* successful in a majority of cases. Also, the distressing, chronic and disfiguring nature of the condition brings into play psychiatric factors whose position—causative or sequential—are a matter of great debate. We are of the opinion that they are not causative.

Simon continues his studies of patch tests with protein allergens in atopic dermatitis. In a recent paper[64] he attempts a correlation of scratch and patch tests to ragweed pollen, blue grass pollen, human dander and hen's egg. In a significant percentage of cases that gave urticarial reactions to these substances, a positive patch test reaction in the form of "characteristic atopic reactions to patch tests" was obtained. The main criticism that we have of this work is the clinical and etiologic interpretation of these patch test reactions. The histology of atopic dermatitis is subtle; preponderant opinion is that, except in infants and young children, it is located in and about the capillaries of the papillae of the true skin and that epidermal changes are secondary to such a process and to adventitious factors like scratching and medicating. It is undoubtedly true that atopic subjects show more such positive patch test reactions than normal subjects but the question arises whether this is, at least in part, due to the greater susceptibility of atopic skin to sweat gland occlusion effects as was shown by Sulzberger, Hermann and Zak.[70]

The word "eczema" is still a thing of many meanings. To non-derma-

tologists, eczema is often mainly a clinical concept which in their minds is not different from dermatitis, particularly when there is erythema with oozing and crusting. In some dermatologic circles eczema has a clinical qualification in the requirement of papulo-vesicular changes with erythema and a histopathologic qualification in the requirement that the quintessential pathology (spongiosis) be in the epidermis. In young children and infants atopic dermatitis fulfills these requirements but not in adolescents and adults. Hill[32] finds wool a common cause of "eczema" in children. However, Hill's method of testing is unorthodox and his results therefore cannot be compared with those of orthodox patch or scratch tests in reports of other authors. For, Hill patch tests for wool by first scraping the skin "in order to remove at least part of the protective keratin layer" and then leaves the patch on for "several days." Fourteen out of forty test subjects reacted to such a test. While under clinical conditions a combination of friction plus contact with wool is probably to blame for the production of the reaction, one may doubt whether abrasion of the skin before doing a patch test really imitates the natural conditions of contact more closely than a simple patch test; for after such abrasion, application of an unsterile, barbed fiberlike wool may possibly irritate the skin in some of the cases in a non-specific manner. What Hill's results might be interpreted to prove is that wool mechanically irritates some skins and especially already damaged skin. This alone would be reason enough to council avoidance of wool in any dermatosis, but particularly in atopic dermatitis. But in addition Hill states that wool is a cause of eczema by a sensitization mechanism in patients with atopic dermatitis. In view of what was said above regarding the occurrence of real eczema in the strict dermatologic sense in infants and young children, one of us (R.L.B.) agrees with Hill's theory that many cases of wool dermatitis in infants are probably contact atopic dermatitis, i.e., an atopic dermatitis evoked by an allergen which elicits the atopic response (not an eczema) by contact; and the other (M.L.) disagrees and would say that in the event of an epidermal sensitization upon atopic dermatitis, the dual condition is coincidental.

Epstein and Palecek[18] present a statistical investigation and statement on atopic dermatitis in a first paper of what appears will be a series on infantile eczema. Of 247 patients living in a rural environment, they found (a) that 75 per cent gave multiple positive wheal reactions to scratch tests with common food and environmental inhalant allergens, (b) that reactions to foods were more frequent during the first six months and to environmental inhalant allergens thereafter, (c) that egg, wheat, potato and milk gave the greatest number of food reactions in skin tests whereas cattle, horses, feathers, house dust and wool allergens were most frequent reactors of the inhalant variety of materials, (d) that the incidence of reactions to egg fell and that to wheat and potato rose in the first and second years of life, and finally (e) that clinical activity of atopic dermatitis was greater in patients with urticarial skin reactions to these allergenic substances than in non-reactors. Epstein and Palecek make no direct reference to therapeutic implications of the findings but their discussions suggest that they believe that eliminations of substances that give positive reactions are helpful.

Studies of atopic dermatitis that purport to be able to discover precise causes and end with a statement of good results in *large percentages* from treatment based on the avoidance of alleged allergenic causes have always been of great interest to us because we have been unable to duplicate such

results, except in a small proportion of our own cases. Such a study is that of Rowe and Rowe.[57] These authors followed 100 consecutive cases of atopic dermatitis and are convinced that they discovered causes in these cases in the following distribution: foods alone 44 per cent, inhalants alone 15 per cent, foods and inhalants together 41 per cent. Note the 100 per cent etiologic resolution. Treating from what they considered cause, good or excellent results in 84 per cent of cases is claimed. The criticism we have of such report is the sense of sureness the workers have in the accuracy of their testing as a revelation of cause and the confidence they have in benefit derived from their therapeutic measures. To treat atopic dermatitis with desensitization, elimination diets, vaccine therapy and topical medicaments simultaneously for months to years and then claim benefit as stemming largely from the "specific" part of the treatment is in our opinion open to criticism. The natural history of atopic dermatitis is one of exacerbations and remissions and in any prolonged period of observation improvement will be noted at times without any treatment at all.

The following statements are quoted verbatim to show the length of treatment necessary and the results which can be expected according to Rowe and Rowe: "Follow-up study has revealed that elimination of offending foods is necessary for periods varying from six months to as long as five years in many patients, and frequently establishes tolerance in from six months to five or more years. When inhalant allergy is the sole or a contributing cause, desensitization therapy is often necessary for one to three years. In some cases the degree of relief at the end of the first year was only 50 to 75 per cent and increased significantly during the second year of our control."

In this connection it may be worthwhile to submit to the readers once more a summary, published elsewhere[2] of some of the more important nonallergic features which are found in patients with atopic dermatitis and which, of course, may play a role in influencing the clinical events. The summary is as follows:

(a) A tendency to local vasoconstriction (white dermographism) rather than local vasodilation upon stroking of affected skin areas.

(b) A tendency to low blood pressure and low blood sugar tolerance curves.

(c) A tendency to disturbances in the sweat secretion due to plugging of sweat pores and consequently increased itching and flare-ups of the eruption upon perspiration, physical exercise and exertion and emotional stress.

(d) A tendency to increased itching after rapid changes in environmental temperature and topical application of greasy and oily medicaments.

(e) A tendency to flare-ups after exposure to woolen garments and to soaps.

(f) A tendency to flare-ups after acute non-febrile infectious diseases (e.g., colds) and after certain immunization procedures (particularly in infants and young children).

(g) A susceptibility to superimposed secondary infections with certain viruses (herpes simplex, vaccinia).

(h) A tendency to rapid improvement upon changes in environment, especially hospitalization and removal to sunny, dry and hot climates.

It seems to us that application of the allergic concept to atopic dermatitis cases has advanced our ability to manage these cases to a certain degree, but that very little if anything further is to be expected from this approach

as far as *future* progress is concerned. Certain abnormalities in the physiologic mechanisms in atopic dermatitis which have been described in recent years appear to offer a much more fruitful approach. Among these, we wish to call attention to the sweat difficulties which were described by Sulzberger, Herrmann and Zak,[70] and to the recent article of Eyster, Roth and Kierland.[20]

The latter group brought scientific proof of the existence of a tendency to vasoconstriction of the peripheral vascular system in patients with atopic dermatitis. This fits in very well with the previously known clinical finding of "white" dermographism in such patients.

Such studies on the physiologic disturbances in atopic dermatitis patients are, in our opinion, also much more likely to bring us further along in assessing the role of emotional factors than the rather fantastic interpretative reports of individual cases with which the medical literature is being flooded by observers who are either not trained in scientific investigation or who believe that in the field of atopic dermatitis investigation scientific criteria are unnecessary.

Another welcome physiologic approach to problems of atopic dermatitis and other dermatoses is the method of Seitz and Shipley[59] for simultaneous recording of psychiatric interviews and galvanic response, a method which is apparently based on changes in electrical conductivity due to changes in sweat secretion.

The possibility that sensitization to infectious microörganisms, especially those encountered in upper respiratory infections, may play an important role in some cases of atopic dermatitis has been considered by various investigators. Rostenberg, Vicher and Brunner[55] carried out a bacteriologic and immunologic study and concluded that there is no evidence either for or against bacterial sensitization playing an etiologic role in atopic dermatitis. The results of their study in twenty-two patients with atopic dermatitis certainly speak against a specific role of the bacterial agents but they do not contradict the clinical evidence, seen every day, that non-febrile upper respiratory infections cause flare-ups of atopic dermatitis, probably on a non-specific basis.

Following our discussion of the paper of Rowe and Rowe,[57] we wonder what to say of Lowenthal's claim[41] of 83 per cent subjective and objective improvement of various eczematous and eczematoid conditions ("Eczema-Dermatitis") upon the exhibition of sulfapyridine. If the results of these two studies were confirmed, we would have two methods at our disposal which "cure" 84 per cent and 83 per cent respectively of cases of atopic dermatitis. According to Lowenthal, infantile eczema, atopic dermatitis, acute endogenous eczema, chronic endogenous eczema, pregnancy eruptions, residual eczema after contact dermatitis, nummular eczema, autosensitization eczema, infectious eczematoid eczema, and even patch tests, all seem to fall before sulfapyridine in more than eight out of ten times. The trouble with such studies lies again in diagnosis—which often cannot be certain—and the natural course of any disease which can *never* be known in particular instances. If sulfapyridine is so good, therapy of cases of eczema-dermatitis is so simple as to practically eliminate the need for search for other therapeutic measures!

A preliminary report by Sulzberger and Witten[72] describes the use of an ointment containing compound F (17-hydroxycorticosterone-21-acetate) 25 mg per gram of base in eight patients with atopic dermatitis. One patient was much better, five were slightly better and two were unimproved after application of compound F ointment. It appears then that while topically

applied cortisone is without value in atopic dermatitis, ointments containing compound F are worthy of further trial. We have used ointments containing 10 mg compound F per gram of base and our experience has also been very encouraging in some cases.

The use of corticotropin and cortisone in atopic dermatitis from the infantile eczema stage to the adolescent stage is critically reviewed by Glaser.[23] He adds a number of worthwhile observations to the now well known fact that corticotropin and cortisone in adequate doses suppress atopic dermatitis in children as well as adults. One child is reported to have developed an attack of asthma while on a dose of corticotropin which was adequate to suppress its atopic dermatitis. This suggests that, at least in some patients, a larger dose of corticotropin is required to suppress asthma than atopic dermatitis when they occur simultaneously. Another child developed a mild nephrosis while on corticotropin therapy, suggesting that the hormone probably has no influence on the *etiologic* factors in nephrosis although the drug is useful in treating the edema due to this disease. Glaser concludes that corticotropin and cortisone therapy should not be employed until all other forms of orthodox therapy have been tried without relief and these drugs should not be used even then unless the patient is urgently in need of relief.

URTICARIA

The type of investigation that the problem of urticaria demands, namely, rigidly controlled studies, is seen only rarely in the recent literature. Next to atopic dermatitis, some of the most absurd therapeutic claims, *post hoc propter hoc* conclusions and fancy psychiatric interpretations are made with respect to urticaria.

Urticaria or urticarial lesions of many types and of very many different causes are seen in clinical practice. To mention a few clinical types, there are acute urticaria, chronic urticaria, urticarial dermographism, angioneurotic edema, papular urticaria and urticarial lesions as part of the eruptions of many dermatoses like erythema multiforme, atopic dermatitis, zoonoses, dermatitis herpetiformis, et cetera. The condition that exercises most workers is chronic urticaria, i.e., the clinical form that consists of often daily, continual, unpredictable eruption of hives for months and years.

Cohen and Criep[12] found endameba histolytica in the stools of nineteen of twenty-eight patients with chronic urticaria and/or angioneurotic edema. All nineteen patients became free of their urticaria when they were subjected to anti-amebic treatment with carbarsone, diodoquine and emetine. An interesting observation is reported in that many patients showed a sudden and acute exacerbation of their eruption during the second and third day of emetine therapy. The authors attribute this, in our opinion correctly, to the absorption of larger quantities of allergenic material liberated by the sudden destruction of many organisms.

A team of investigators who should be congratulated on finding causal agents in a high percentage of cases of angioneurotic edema are Bruun and Dragsted.[8] We envy their ability to find causes "unquestionably" in fifty-three of ninety-four cases while in another twenty cases etiologic diagnosis was made but not corroborated beyond doubt.

Urticaria due to inhalant allergens always has been a difficult subject to investigate. Waldbott and Merkle[75] point out that most surveys of the urticaria problem do not even mention the pollen group of inhalants as possible causes. They report twenty-six cases of urticaria in which clinical

evidence pointed to pollen as being the principal causal factor. In twelve cases the urticaria was confined to the pollen season and in fourteen cases secondary factors are thought to have been the cause of extension of the duration beyond the pollen season. In many of the patients, attacks of urticaria were reproduced by insufflation of the causal pollens into the nasopharynx. Hyposensitization treatment with the pollen is said to have cleared the urticaria as a rule after two to three injections. Too large a dose of pollen extract aggravated the disease or prevented the beneficial effects of the hyposensitization therapy.

We feel that their paper represents an addition to our knowledge of urticaria. However, we are astonished by the authors' finding of twenty-six cases of urticaria which seemed to coincide with the pollen season, when we ourselves recall seeing only one such case in many years of observation, and we wish to call the attention of the readers to the difficulties inherent in assaying therapeutic procedures in any disease which undergoes "spontaneous" fluctuations such as urticaria. For example, Waldbott and Merkle state "some patients remained symptom-free throughout the season, whereas the hives recurred in others after one to two days and required additional injections." How can one tell whether hyposensitization in urticaria is effective for one or two days when there are often spontaneous remissions for two or three days?

Weil and Rogers[76] investigated a patient with allergic reactions to simple aliphatic acids. Sensitivity was of both the eczematous and the urticarial type but there was no complete overlapping of the sensitivity spectrums in the two types of allergic responses. The specificity of the reaction was to the acid as such and not to acetate or acyl radicals.

Cohen[11] recounts six cases of chronic urticaria which were successfully managed by injections of moccasin snake venom. Whatever the merits of this non-specific treatment, we miss in the case history reports mention of search for drug causes. If we were to be asked what are the causal possibilities in chronic urticaria, we would say that in the large majority of our own cases we have been unable to discover the causal factor or factors. Moreover we would say that there is no proof that all or even the majority of cases of chronic urticaria are based on allergic mechanisms. In the *minority of cases* in which we have been able to find the etiologic factor or factors, perhaps 75 per cent were due to or maintained by the ingestion of simple chemicals (drugs: penicillin, salicylates, et cetera; chemical agents in processed foods, et cetera), 20 per cent were due to or maintained by focal infection (bacterial) and infestation (e.g. helminthic) and finally 5 per cent were due to or maintained by foods. We could say further that persons who have chronic urticaria caused by a food sometimes will themselves be able to specify the very food, and that they will state definitely that it is, say, mountain oysters or kumquats and not vaguely protein or citrus fruit. Focal infection even when discovered is rarely eradicable except in the case of teeth and sometimes the tonsils or gall bladder. Finally, search for and elimination of drug and other simple chemical causes is the most profitable and rewarding activity in the cure of chronic urticaria. To this end a wide knowledge of the multitudinous sources of occult ingestion of simple chemicals and their potential for inciting chronic urticaria, and an artfulness in taking a drug history are required.

PROGRESS IN ALLERGY

DRUG ERUPTIONS

The only thing that keeps pace with the present-day prolific production of new drugs is the occurrence of eruptions and other reactions from them. If one may venture a facetious prediction, it may occur that eventually we shall have specific chemotherapeutic or antibiotic agents for every disease and then our only problems will be to treat the diseases caused by the many different drugs.

If anyone still doubts the reality and seriousness of drug eruptions, contemplation of atabrine dermatitis should be persuasive. Shamberg[62] presents a three and one-half to seven-year follow-up of nine veterans of the last war and describes active inflammatory cutaneous changes, pruritus, permanent alopecia, cutaneous atrophy and anhidrosis as some of the effects they still suffer. The mechanism of such persistence of cutaneous pathology so long after the drug has been ingested is most obscure. However, a parallelism is found in the persistence of skin changes after the administration of arsenic. One possible explanation, in our opinion, is that the drug may not be completely eliminated and may not be eliminated for years. In view of the excellent results which have recently been achieved with prolonged administration of atabrine in chronic discoid lupus erythematosus, it should be stressed here that *severe* side effects as described by Shamberg apparently occur only in persons who ingest the drug while living in tropical climates.

A paper by Robinson[50] recounting a case in which clinical analysis suggested Hodgkin's disease, but which proved to be caused by mercury, illustrates the protean character of drug eruptions. It is well to recall Sulzberger's remark that drugs and their effects are replacing syphilis as "the great imitator."

Another illustration of this is contained in an article by Usher[73] in which Loeffler's syndrome occurred in a case of iododerma and from the clinical course it is probable that iodine caused both conditions.

Another instance of association of Loeffler's syndrome with a cutaneous eruption is reported by Jones and Ogle.[34] The etiologic factor was apparently not discovered in their case.

Again the variety of drug eruptions, both as to type and as to drug cause is illustrated by a report of Welsh and Goldberg[77] of a fixed eruption from aureomycin.

The significant incidence of undesirable allergic side effects due to conventional penicillin therapy has stimulated a widespread search for a hypo-allergenic form of penicillin. The evaluation of these "hypo-allergenic" penicillins is obviously an extremely difficult task—even for large pharmaceutical firms which have at their disposal more than adequate clinical facilities for assaying the various properties of *new* drugs. However, the scientific appraisal of a hypo-allergenic material which will be used as widely as a penicillin preparation demands more than adequate facilities—it requires facilities which are probably impossible to provide! Dermatologists as a group are very well acquainted with this problem in connection with the studies to establish the sensitizing capacity of eczemaogenic allergens, an everyday problem in dermatologic practice. The two volumes which have been published on the hearings of the House Select Committee on "Chemicals in Foods and Cosmetics" bear testimony to this as far as new cosmetic preparations are concerned.

The task is even harder when one looks for a "hypo-allergenic" penicil-

lin. For the same penicillin preparation which does not elicit reactions in patients having one type of allergic reaction to penicillin may well cross-elicit severe and even potentially fatal reactions in patients with another type of allergic response to penicillin. Who knows whether the chemical grouping in ordinary penicillin which is the cause of urticarial allergic reactions is the same as the one which is the cause of an allergic reaction which expresses itself in eczematous, anaphylactoid, "id"-like or exfoliative dermatitis reactions? Furthermore, even if there were a "hypo-allergenic" penicillin which would not cross-elicit with ordinary penicillin in any form of these allergic reactions, would not the "hypo-allergenic" penicillin itself have the potentiality of engendering such allergic reactions? These are only two of the many important questions which arise in connection with the evaluation of allergenic properties of drugs in general.

Stroud[66] reports an incident in a physician patient who developed an anaphylactic shock—we would prefer to call it an anaphylactoid shock—within a minute after an injection of a "hypo-allergenic" penicillin (1-ephenamine penicillin G). There was a history of an attack of nausea and vomiting after an injection of procaine penicillin eighteen months previously. Those interested in this subject will find a number of other pertinent references in Stroud's article. The many different mechanisms which might underlie the various forms of penicillin reactions and which must be considered in relation to "hypo-allergenic" penicillins are discussed in papers by Reyer[49] and Goltman.[25]

THE ALLERGY OF INFECTIONS

Some of the clearest expressions of allergic mechanisms can be found in the allergic transformations that regularly occur in response to infection. The negative Schick test, the positive tuberculin, Frei and trichophytin test, the Widal reaction and other serologic reactions are all tests of the existence of specific acquired alterations in the capacity to react. And, upon analysis, many clinical expressions of infectious diseases like tuberculosis, leprosy, syphilis, the mycoses, virus and rickettsial infections are based on allergic reactions.

Sonck[65] reports four cases of milker's nodules with secondary eruptions which are termed allergic.

The pertinent information regarding immunologic changes which take place in the allergy of infection are summarized in a paper by one of us[38] which contains a long discussion of a unitary theory of the allergy of infection. In this account, following a division formulated by Sulzberger, infectious processes are divided into two great immunologic groups, namely, (a) primarily toxic diseases, and (b) primarily sensitizing diseases. Regarding primarily sensitizing diseases, Leider claims that all expressions of these diseases are allergic, including the initial lesion which almost always appears chancriform. Subsequent lesions which follow after the formation and healing of the chancre are new allergic events resulting from additional or successive or multiple allergic transformations. In a sense all diseases of sensitization may have primary, secondary, tertiary, and perhaps still later stages. There is, in his opinion, an error in reasoning when secondary or subsequent eruptions (including the "ids") are called allergic whereas primary lesions are not. It is incorrect to assume that the "allergic" phenomena of infection are always those in which organisms are sparse or absent. The latter condition is not absolute and

some plainly "allergic" lesions or "ids" teem with organisms, e.g., syphilids of the secondary stage.

Danbolt,[15] in whose clinic Kveim worked upon the cutaneous test for sarcoidosis with a suspension of sarcoid tissue, reviews the whole history of the test and brings up to date his experience with it. The relative specificity of the test for sarcoidosis is affirmed again. In a short critique of etiologic interpretation from the test, Danbolt argues that the Kveim reaction is the expression of an allergic reaction to specific substances present in sarcoid tissue suspension, and that an infectious substance, e.g., a filtrable virus, is probably responsible for production of these substances.

A paper by Rostenberg[53] attempts to reopen the question of the role of the tubercle bacillus in sarcoidosis. This is not the place for a long discussion of the pros and cons of Rostenberg's arguments against the tuberculous etiology. It is our understanding that the classical work of the school of Joseph Jadassohn which demonstrated the frequent absence of cutaneous sensitivity to tuberculin (tuberculin anergy) in sarcoid patients was done to show that there *could* be an etiologic relationship between the tubercle bacillus and sarcoidosis rather than to prove that there was one. This demonstration consisted of evidence that the *lack* of skin reactivity to tuberculin was specific, i.e., that it did not extend to extracts of other microörganisms. Rostenberg takes the view that there is no proof for such a specific anergy to tuberculin, and that even if the anergy were directed towards tuberculin only this peculiar lack of skin response might have been induced by exposure to an immunologically related microörganism—the hypothetical causal agent of sarcoidosis—rather than by exposure to the tubercle bacillus. Since neither Rostenberg nor anybody else has brought forth positive evidence showing the existence of such a causal agent, the entire argument for and against the tuberculous etiology of at least some cases of sarcoidosis must be considered undecided.

The Kveim test, utilizing a material prepared from sarcoid tissue of spleen, was carried out by H. W. Wade[74] in ten patients with the lepromatous form of leprosy and in seven lepromin-positive staff members of a leper colony. The Kveim tests were entirely negative, suggesting that there is no etiologic relationship between sarcoid and leprosy.

Baldridge and Kligman[6] performed experiments with vaccinia virus in guinea pigs which confirm in the experimental animal the well-known simultaneous development of hyposensitivity and hypersensitivity seen in human beings who have undergone smallpox vaccination. For it is well known that those who have been properly vaccinated with cowpox material develop the following:

(a) a hyposensitivity—as shown by their inability to react with the highly inflammatory "take" after eight to eleven days; and
(b) a hypersensitivity—as shown by their ability—which does not exist in those not previously exposed—of developing a mild "reaction of immunity" after two to three days.

Baldridge and Kligman demonstrated in guinea pigs that desensitization with vaccinia virus does not result in loss of immunity, indicating a dissociation of the processes leading to hypersensitivity and the processes leading to immunity.

MISCELLANEOUS

A very worthwhile investigation of mosquito bite reactions has been started by Rockwell and Johnson.[51,52] They observed very small re-

actions resulting from irritation alone, and allergic reactions of the urticarial, tuberculin-type and eczematous forms. They conclude that while there is evidence that multiple allergens are involved in the mosquito bite reaction, extracts of various parts of the mosquito produce similar reactions in sensitive individuals.

The etiologic factors of papular urticaria, an eruption which consists of wheals and papules mainly on the exposed parts of the skin, have been a subject of discussion for many years. The recent literature contains much evidence that in many patients this disease is caused by the bites of insects. Shaffer, Jacobson and Pori[61] assembled clinical, epidemiologic, allergic, histologic and therapeutic evidence that many cases of the disease are due to allergic sensitization to materials encountered in the bites of various insects. They suggest the possibility that many cases of papular urticaria represent a phase in the development cycle of the individual's response to insect allergen. Under usual circumstances the tuberculin-type sensitive phase is either transient or ill-developed. In some patients with papular urticaria this phase persists and is severe and predominates the clinical picture.

The subject of allergic hypersensitivity to steroid substances is discussed by Meltzer[42] on the basis of skin tests by the Zondek-Bromberg method in nineteen cases. From a small series of cases of acne vulgaris, it is suggested that there may be some cases of acne vulgaris in which steroid hormones are acnegenic due to their *allergenic* activity rather than their purely hormonal activity. In such cases specific hyposensitization with the steroid material is thought to be beneficial. Our own experience has taught us that skin tests by the Zondek-Bromberg method are not easy to interpret, that utmost caution must be applied in their interpretation, and that a small series of cases is not adequate to draw even tentative conclusions. However, Meltzer's work is thought-provoking and more extensive studies in acne cases appear warranted.

The modern tempo of medical and general scientific advance is very fast. The many new chemotherapeutic and antibiotic agents of recent years and the powerful hormones like corticotropin and cortisone go through a relatively short period—similar to a shakedown cruise—during which the medical profession orients itself regarding the benefits and ill-effects which are to be expected from each new drug. Then further investigation settles down to a carefully controlled long-term scientific evaluation of those of the new drugs which appear to be worthy of further trial. Thus most drugs find their proper niche. Not so with psychosomatic treatment of all sorts of ailments including allergic and nonallergic dermatoses. Here part of the medical profession appears to have embarked on a prolonged shakedown cruise with no safe landing in prospect. In this field the most elementary rules of statistics and of scientific proof seem not to be compelling to some who are carrying on and are publishing work which deals with psychosomatics. Unfortunately some articles that discuss the possibilities of psychosomatic causation of disease with judicious conservatism and simple logic seem to fall on deaf ears.

Among the more conservative recent papers on the general problem of emotional factors in allergic dermatoses is that of Rothman and Walker.[56] Limiting themselves to consideration of psychosomatic cause and effect in allergic eczematous contact dermatitis, urticaria and atopic dermatitis, these authors conclude that only in atopic dermatitis do emotional factors have great significance. The mechanism is a lowering of the threshold for itching which in turn leads to increased rubbing and scratching. In

cholinergic urticaria, attacks are precipitated by emotion but an abnormal hypersensitivity to acetylcholine is the ultimate basis for the clinical event of whealing. In chronic urticaria where no allergen can be demonstrated, the question of both allergic mechanism or psychic origin is unanswerable, and finally, allergic eczematous contact dermatitis is never of psychic causation.

We wholeheartedly endorse the attitude of Rothman and Walker on the role of psychosomatic factors in the dermatoses discussed by them and we recommend detailed reading of their paper to all those who are interested in this important subject. There is only one technical statement contained in their paper which we believe is incorrect, namely, that dermographism and cholinergic urticaria can be passively transferred. While this may be so in exceptional cases, proof is lacking in the large majority of cases.

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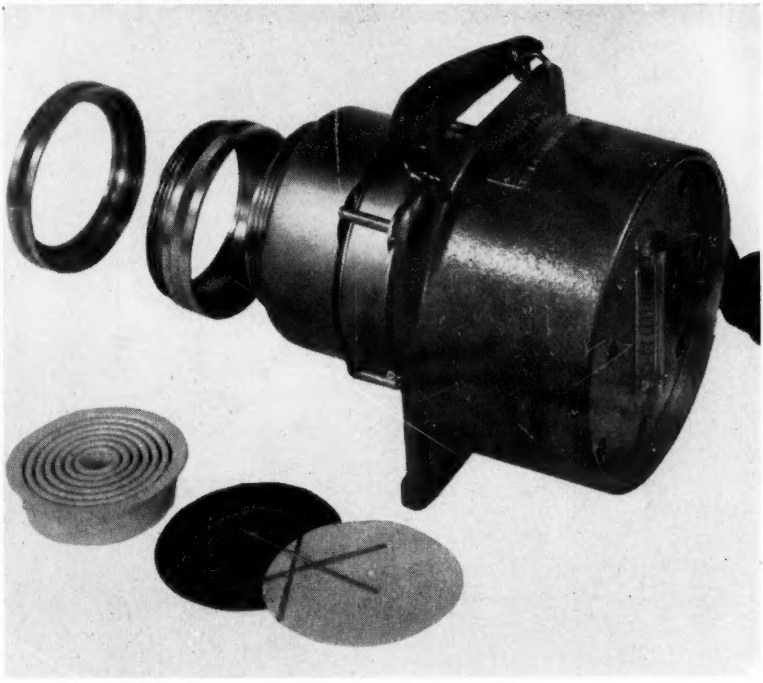
962 Park Avenue, New York 28, N. Y. (Dr. Baer)
820 Caton Avenue, Brooklyn, N. Y. (Dr. Leider)

Industrial Allergy

AIR AND SMOKE SAMPLERS

Since the rapid development of industrial plants throughout the United States for the making of new chemicals and other air pollutants which are a menace to health and frequently the cause of aggravating respiratory allergies, industrial allergy is becoming increasingly important. It is possible that those interested in air pollution and aerobiology would also be interested in learning of the development of recent air and smoke samplers and their possibilities.



High Volume Air Sampler

With the problem of air pollution being of tremendous importance to municipal governments and industry, The Staplex Company, 68-62 Jay Street, Brooklyn 1, New York, through permission from The United States Atomic Energy Commission, now makes available a high volume air sampler unit for general use.

This unit was developed in the laboratories of the New York Office of AEC and has been manufactured in large quantities by Staplex for this Commission Agency.

The prime purpose of the unit is sampling large volumes of air for particulate matter by means of a filter paper. The unit has been used successfully to sample air containing particles as small as one hundredth of a micron in diameter.

The high volume air sampler employs a turbine type blower, is designed for 24-hour sampling, and has a rugged cast aluminum housing (keeping the weight down).

The high volume air sampler employs a turbine type blower; it is designed for 24-hour sampling; has a rugged cast aluminum housing (keeping the weight down).

The Staplex Company reports that this high volume air sampler has become quite a necessity in maintaining modern health standards, and many companies and municipalities are purchasing the samplers for the wide and practical service they offer.

Automatic Smoke Filter

Upon receiving the following information from the Research Appliance Company, Box 413, West View Road, Pittsburgh 9, Pa., correspondence has been carried on with the President, Mr. Elmer E. Fleck, concerning the possibility of modifying the smoke filter so that it would be an efficient pollen collector. Mr. Fleck has

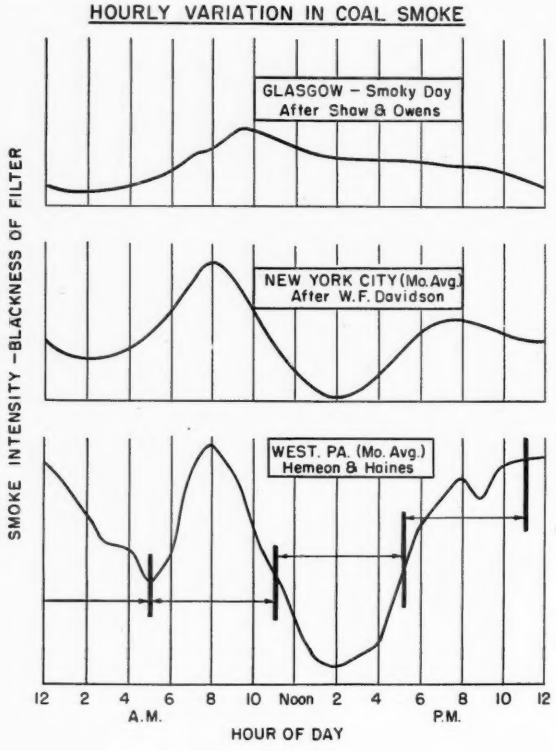


Fig. 1.

promised to attempt to develop the automatic smoke filter for use in sampling pollens. This unit was designed and built with the co-operation of Mr. W. C. L. Hemeon of the Industrial Hygiene Fellowship of the Mellon Institute of Pittsburgh.

This instrument was described in a recent publication "Instruments for Automatic Air Pollution Measurements" by W. C. L. Hemeon, Proc. Air Poll. & Smoke Prev. Assn., P. 115, 1951.

The filter paper method for measuring coal smoke is an arrangement in which the air is aspirated through the pores of white filter paper for a fixed time period.

The resulting black spot is evaluated by reference to a standard scale of blackness. This is the principle of the Owens Automatic Smoke Filter, devised by the late J. S. Owens and widely used in Great Britain.

This improvement has advantages over other dust collectors since it can be arranged for aspiration of much larger quantities of air through one spot so that

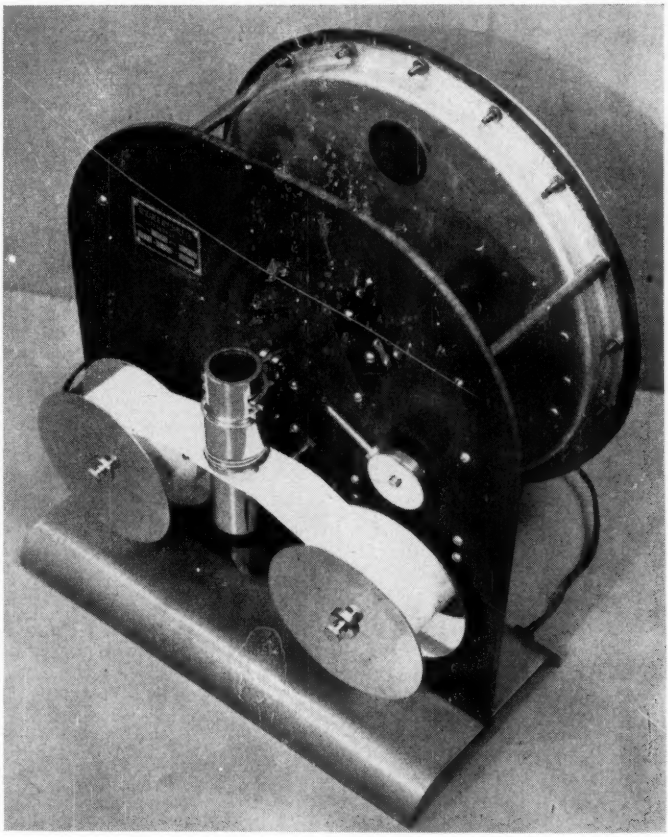


Fig. 2.

besides blackness measurements, it would also become possible to analyze the filtered sample by chemical or physical methods.

The high frequency sampling schedule of the Owens Automatic Filter (two to five times per hour) results in the disclosure of interesting characteristic variations in hourly smoke intensity. In Figure 1 this variation is shown in data reported by Owens himself, by W. F. Davidson, and in some data obtained by our own laboratory. Although obtained years apart (over twenty-five years) and in different parts of the world, the similarity is striking.

The instrument, illustrated in Figure 2, aspirates air at the rate of approximately ¼ cu. ft. per minute through a 1-inch diameter circle of filter paper which is

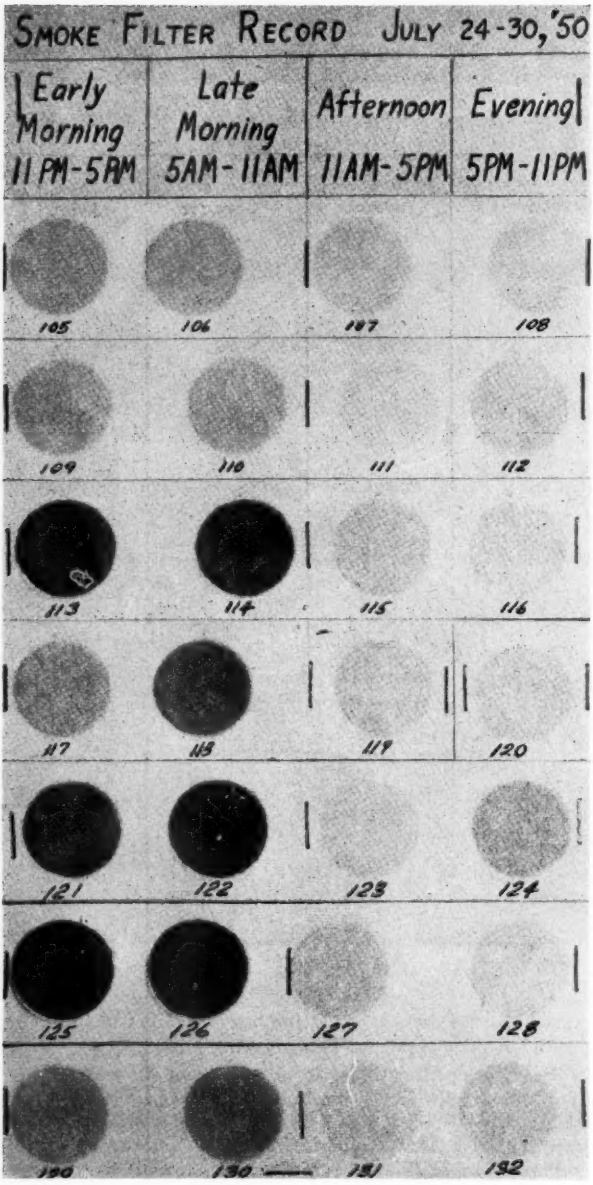

SMOKE FILTER RECORD JULY 24-30, '50
Early Morning 11 PM-5AM
Late Morning 5AM-11AM
Afternoon 11AM-5PM
Evening 5PM-11PM
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Fig. 3.

supplied as tape from a spool. The upper motor makes one revolution each six hours, and at the proper time operates a micro-switch which energizes a solenoid and the windup motor, thus shifting the position of filter paper tape in preparation for the next sample.

The air pump is very quiet and is designed as a simple lowspeed diaphragm pump. Figure 3 shows a record of several days obtained by this instrument, and a typical variation in smoke intensity—relatively high intensity at night and low intensity during sunlight hours.

Evaluation of the spots is effected in three ways: (1) the blackness is determined according to an arbitrary 1-2-3 scale, as originally described by Owens; (2) an optical evaluation with a light meter is made, and this can be done either by measurement of reflected light, or by measurement of relative light transmission. In this instance we employ light transmission because the apparatus for it is cheap and simple; (3) a third method of evaluation involves chemical analysis for any element, or radical that may be of interest in a particular locality.

Any suggestions concerning the conversion of this sampler into a pollen sampler will be appreciated, and detailed information can be obtained from Mr. Elmer E. Fleck, President, Research Appliance Company, Box 413, West View Road, Pittsburgh 9, Pa.

REPRINTS AVAILABLE!

There have been numerous requests for reprints of the special article "Chemical and Immunological Properties of Timothy Grass Pollen Extracts and Problems of Standardization" by R. Augustin Friedmann,* which appeared in the September, 1952, issue of *Quarterly Review of Allergy and Applied Immunology.*

The author has devoted much of her time to the standardization of pollens and presents a critical review of the previous methods used, with a refreshing new approach to the problem. There are 139 references.

Reprints of this fine article may be obtained by directing your order to Mrs. Dorene Dahl Caldwell, *Quarterly Review of Allergy and Applied Immunology,* 401 LaSalle Medical Building, Minneapolis 2, Minnesota. Price per reprint, 50 cents.

Mrs. Friedmann is a full-time rsearch worker for the Asthma Research Council.

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*From the Department of Allergic Disorders (Director, Dr. John Freeman), The Wright-Fleming Institute, St. Mary's Hospital, London, England.

News Items

WHO IS WHO IN ALLERGY

The new directory, *Who is Who in Allergy,* will be published under the auspices of the International Association of Allergology. The Editor is Dr. Egon Bruun, President of the Danish Society for Allergological Research and a member of the Executive Committee of the IAA. Dr. Brunn may be reached at 8 Gersonsvej-Hellerup, Copenhagen, Denmark.

With the founding of the International Association of Allergology, contact has been made among allergists the whole world over. As a means of promoting co-operation, it has been decided to publish a *Who is Who in Allergy.*

This handbook will contain lists of all the existing national allergy associations and their members. Through this handbook allergists will be enabled to make the acquaintance of any allergist they wish to contact. It will also provide a means of assisting allergy patients who would like to know recognized allergists in countries they may visit.

It will contain information of all the existing national allergy associations—the education and training, qualifications, posts of special responsibility, membership, and official positions of each member together with his professional address and hours of consultation.

The publication will appear in loose-leaf form and will be kept up-to-date by the issuance of addenda when necessary.

Any form of nationalism or bias will be rigorously excluded. Each doctor will be allowed to decide whether his biography is to be printed in English, French, German or Spanish.

Members of all allergy associations throughout the world will be receiving a questionnaire. Submitting biographical data involves no obligation to purchase the book. Since it is published under the auspices of the IAA, it is most important that it is as complete as possible. By filling in and returning the questionnaire in the envelope provided, you will be helping international co-operation among allergists.

The publisher is Ejnar Munksgaard, International Bookseller & Publisher Limited, 6 Norregade, Copenhagen K, Denmark.

AMERICAN ACADEMY OF ALLERGY

The Program Committee and the Committee on Local Arrangements are making arrangements for the next annual meeting of the Academy, which will be held at the Hotel Statler in Boston on February 26, 27 and 28, 1953.

Dr. Walter S. Burrage, President of the Academy, 208 E. Wisconsin Avenue, Milwaukee 2, Wisconsin, requests that those who have not submitted titles and abstracts of their papers as well as a statement of presentation time, which should not exceed ten minutes, please do so as soon as possible. All papers presented on the program must be submitted to the Editor of *The Journal of Allergy* for publication.

AMERICAN COLLEGE OF CHEST PHYSICIANS 19th ANNUAL MEETING

The Nineteenth Annual Meeting of the American College of Chest Physicians will be held at the Hotel New Yorker, New York City, May 28-31, 1953.

Physicians who wish to present papers at the meeting should submit titles and abstracts to Dr. Arthur M. Olsen, Chairman, Committee on Scientific Program, American College of Chest Physicians, Mayo Clinic, Rochester, Minnesota.

NEWS ITEMS

AMERICAN ACADEMY OF DERMATOLOGY AND SYPHILOLOGY

The eleventh annual meeting of the American Academy of Dermatology and Syphilology will be held December 6-11, 1952, in the Palmer House, Chicago, announces Dr. John E. Rauschkolb, secretary-treasurer.

Principal sessions will be held in the Palmer House Monday through Thursday, December 8-11, and special courses in histopathology, mycology, x-ray and radium, bacteriology of the skin and research methods of dermatology will be held Saturday and Sunday at the college of medicine, University of Illinois, Northwestern University, Billings Hospital, and in the Palmer House.

CHILEAN SOCIETY OF ALLERGY

At a recent meeting of the Chilean Society of Allergy the following officers were elected for the year 1952-1953:

President: Dr. Zoltan v. Bernath
Vice President: Dr. Alfredo Estevez
Secretary-Treasurer: Dr. Humberto Ricchetti
Directors: Dr. E. Diaz Carrasco, Dr. Ricardo Guzman, Dr. Guillermo Yungue, and Dr. Augustin Estartus.

MICHIGAN ALLERGY SOCIETY

The officers of the Michigan Allergy Society for the year 1952-1953 are as follows:

President: Dr. Jack Rom, F.A.C.A.
Vice President: Dr. Donald S. Smith
Secretary-Treasurer: Dr. Frank F. A. Rawling
Other members of the Executive Committee are: Drs. Homer E. Howes, Sidney Friedlaender, F.A.C.A., and Joseph Shaffer, F.A.C.A.

NEW YORK ALLERGY SOCIETY

The following are the newly elected officers for the year 1953 of the New York Allergy Society:

President: Paul F. DeGara, M.D.
President-elect: Frederick R. Brown, M.D.
Vice President: William B. Sherman, M.D.
Secretary: Murray M. Albert, M.D.
Treasurer: Samuel J. Prigal, M.D.

SOUTHEASTERN ALLERGY ASSOCIATION

The annual meeting of the Southwestern Allergy Association will be held at the Andrew Jackson Hotel, Nashville, Tennessee, May 15-16, 1953. If anyone has a request for a place on the program to present papers, the Program Chairman, Dr. W. Lindsay Miller, F.A.C.A., may be contacted at 1015 Forest Avenue, Gadsden, Alabama. Dr. Clarence S. Thomas, F.A.C.A., President of the Southeastern Allergy Association, is the local Chairman of Arrangements, and may be reached at 706 Church Street, Nashville.

COMMITTEE ON AEROBIOLOGY OF THE AMERICAN COLLEGE OF ALLERGISTS

At the Pittsburgh meeting last April, Dr. L. O. Dutton, F.A.C.A., was appointed by the Board of Regents as Over-all Chairman of the Committee on Aerobiology. Dr. Dutton now reports steady progress in the organization.

The over-all committee has five subcommittees covering the subjects of Mold, Pollen, Bacteria, Industrial Fumes and Dust, and Meteorological factors. They are now planning a long-range program. Its progress depends upon the co-operation of every member of the College. All members who are interested in taking part in any of these subcommittee activities are urged to immediately contact Dr. L. O. Dutton, 616 Mills Building, El Paso, Texas.

NEWS ITEMS

Please watch the ANNALS and Preliminary Program announcements for the time and place of this important committee meeting at the Chicago meeting next April. All those interested are invited to attend and participate in discussions, make suggestions and offer your services.

NEWS ABOUT ACA MEMBERS

Dr. William Kaufman of Bridgeport, Connecticut, read a paper at the December meeting of the American Association for the Advancement of Science, in St. Louis. His paper was entitled "Some Emotional Uses of Foods."

REQUEST FOR REPRINTS CONCERNING STRESS AND THE ADAPTIVE HORMONES

To the Editor:

In perusing current issues of ANNALS OF ALLERGY, we note that an ever-increasing number of its articles deals with problems pertaining to research on "stress" and the so-called "adaptive hormones" (ACTH, STH, corticoids and adrenergic substances, et cetera).

We are writing you because, in our opinion, the success of research in this complex and rapidly developing field largely depends upon the prompt availability and evaluation of relevant publications, a task for which we should like to solicit the assistance of your readers.

In 1950, our Institute has intiated the publication of a series of reference volumes entitled "Annual Reports on Stress" (Acta Medical Publishers, Montreal) in which the entire current world literature is surveyed every year (usually between 2000 and 4000 publications. Up to now, we had to compile the pertinent literature partly from 4000 publications.) Up to now, we had to compile the pertinent literature partly from to us by the authors themselves. Of all these, reprints proved to be the best source of data which we felt deserved prompt attention in our annual reports. Hence, in the past, we have sent out several thousand individual reprint requests to authors of whom we knew to be currently engaged in research on stress and allied topics. Even this procedure did not give us the wide coverage which would be desirable.

It is evident that in order to insure prompt inclusion of publications in the annual reports, these surveys must develop into a co-operative effort between the authors of original papers and the reviewers. This co-operation was greatly enhanced of late by the publication of announcements, in several medical journals, encouraging investigators interested in stress research, to send us their reprints for this purpose as soon as they become available.

We would be grateful if by the publication of this note, you would also bring this problem to the attention of the readers of ANNALS OF ALLERGY.

We are, Sir,

Very sincerely yours,

HANS SELYE, M.D., Ph.D., D.Sc., F.R.S.(C),
Professor and Director of the Institute of Experimental Medicine and Surgery.

ALEXANDER HORAVA, M.D., Co-author of the "Annual Reports on Stress"

P.O. Box 6128
Montreal, Quebec
November 6, 1952

BOOK REVIEWS

MODERN HEADACHE THERAPY. By Arnold P. Friedman, M.D., Physician-in-Charge of the Headache Clinic, Montefiore Hospital; Assistant Professor of Clinical Neurology, Columbia University Medical School; Attending Physician Montefiore Hospital; Associate Attending Physician, Presbyterian Hospital, Neurological Institute,; Area Consultant in Neurology, Veterans Administration, New York. 164 pages, 3 charts. St. Louis: The C. V. Mosby Co., 1951. Price $4.00.

This handbook is up-to-date, practical treatise on headache treatment. Chronic headache is one of the most disturbing ailments the practitioner encounters. The aim of the book is to present principles which will give the best results of treatment. These principles are based upon the more recent physiological and psychosomatic mechanisms involved in headache. Both physical and emotional aspects are considered in the treatment of the patient.

The patient's immediate concern is to obtain relief, while the physician must appreciate the wide variety of disorders which may cause headache. He must endeavor to discover its cause since wrong therapy may be disastrous. In this book, the author presents his experiences derived from an extensive private practice and also from the records of three headache clinics, covering more than 5,000 patients who have been observed and treated during the past six years.

There are nine chapters dealing with diagnosis, treatment, mechanisms of pain, headaches associated with intracranial disorders, headaches due to systemic disorders, migraine headache, psychogenic headache and post-traumatic headache.

Each chapter has extensive references and the index is complete. The practitioner, as well as the medical student, will find the book a basic guide in headache therapy.

R FOR MEDICAL WRITING. A Useful Guide to Principles and Practice of Effective Scientific Writing and Illustration. By Edwin P. Jordan, M.D., and Willard C. Shepard. 112 pages with 26 figures. Philadelphia and London: W. B. Saunders Company, 1952. Price $2.50.

Experienced and successful writers agree that proficiency in the art of medical writing is acquired only by prodigious efforts. With the aid of this little book, writers of scientific articles can express clearly what they mean and can avoid or eliminate those faults in the final manuscript which may cause confusion, and which detract from the full effectiveness of the article. The manual makes no pretense of duplicating the many good books on English composition, grammar and style—but is intended to be of practical value to medical writers in the preparation of their papers.

POISONING. A Guide to Clinical Diagnosis and Treatment. By W. F. von Oettingen, M.D., Ph.D., National Institutes of Health, U. S. Public Health Service, Federal Security Agency, Bethesda, Md. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York, 1952. 506 pages, no illustrations. Price $10.00.

This timely volume has been prepared for quick-reference clinical help. It includes symptoms and treatment of 461 toxic substances, arranged in alphabetical order. The book is divided into four parts—classification, diagnosis, management, and symptoms and treatment of 461 types of poisoning.

Besides the dramatic death from poisoning, the subacute and clinical cases are far

more common and frequently offer serious problems for diagnosis, which in turn determine the proper therapy and prognosis. With the increase of many new chemicals on the market which are used in homes and industry, both acute and chronic incidence of poisoning are constantly increasing. Many of these new drugs produce side reactions of varying severity.

There are hundreds of substances in use today which may give rise to poisoning or produce toxic syndromes which closely simulate infections or functional diseases. This volume helps to differentiate these symptom-complexes. It is a ready aid to the general practitioner and the internist in the diagnosis and treatment of poisoning which is inevitably encountered at some time during his practice. In the listing of the types of poisoning there usually follows one or more references pertaining to the particular potential poison. The book is very durably bound, and comes up to the high standards set by the publishers.

THE NATURE OF THE BACTERIAL SURFACE. A Symposium. Edited by A. A. Miles and N. W. Pirie, with a preface by Prof. Sir Alexander Fleming (Nobel Prize). 179 pages 7 figures. Springfield: Charles C Thomas, 1950. Price $3.00.

The contents of the book represent a symposium of the Society for General Microbiology, held in London April 20, 1949. At this meeting distinguished workers from France, Holland, South Africa, and the United States were invited to make contributions to the symposium. This volume represents the proceedings at this meeting, with a discussion of some of the more important problems. There were 27 contributors. The contents include an introduction by N. W. Pirie, as well as the presentation and discussion of the following subjects: The Surface Structure of Shigella shigae as Revealed by Antigenic Analysis, The Nature of the Surface of Gram-Positive Bacteria, The Osmotic Barrier in Bacteria, On the Mechanism of Adsorption of Bacteriophages on Host Cells, The Status of Some Arguments About the Bacterial Surface, The Nature of Bacterial Surfaces, Capsule Formation in the Pneumococcus, and Bacterial Surface, Flagella and Motility. There are 12 beautiful plates.

Biochemists have recently and properly invaded the field of pure bacteriology as it is now generally recognized that practically all phenomena exhibited by bacteria are biochemical processes. It is due to the biochemist's appreciation of the simple logical fallacies which have been manifest in the field for some time. When arranging the symposium a committee deliberately chose as a title the broad word "surface" realizing that any attempt to define the accurate differences between the various superficial structures would be of no advantage. They stick to the relevant discussion of considering "any part of the organism that is likely to make direct contact with components of the environment." A discussion of the behavior of bacterial viruses is also presented.

The various articles are followed by a most complete reference list. The discussions throughout bring out controversial points which makes the book more interesting. Any scientist or medical student, or general practitioner should gain a better understanding of the behavior of bacteria by studying such a text.

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IN MEMORIAM

NEWS ITEMS

PROGRESS IN ALLERGY

ANNALS of ALLERGY

PUBLISHED BY THE AMERICAN COLLEGE OF ALLERGISTS

Graduate Instructional Course—April 24-26, 1953
and
Ninth Annual Congress—April 27-29, 1953

Conrad Hilton Hotel (The Stevens), Chicago

November-December
1952

Volume 10, Number 6

Published Bimonthly

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